

EXHIBIT 1

[Home \(/\)](#) > [News \(https://www.sandoz.com/news\)](https://www.sandoz.com/news) > [Sandoz announces further progress on its biosimilar pipeline, with release of positive results for denosumab integrated Phase I/III clinical trial \(https://www.sandoz.com/news/media-releases/sandoz-announces-further-progress-its-biosimilar-pipeline-release-positive-results-denosumab-integrated-phase-iii-clinical-trial\)](https://www.sandoz.com/news/media-releases/sandoz-announces-further-progress-its-biosimilar-pipeline-release-positive-results-denosumab-integrated-phase-iii-clinical-trial)

Sandoz announces further progress on its biosimilar pipeline, with release of positive results for denosumab integrated Phase I/III clinical trial

Sep 19, 2022

- *ROSALIA study met primary endpoints, confirming proposed biosimilar denosumab matches reference product in terms of pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity in postmenopausal women with osteoporosis*
- *Osteoporosis accounts for 8.9 million bone fractures annually, including debilitating hip fractures – a number set to increase substantially over next two decades¹*
- *Positive trial results follow filing acceptances for two other proposed Sandoz biosimilars, adalimumab HCF and natalizumab, by both EMA and FDA*

Basel, September 19, 2022 – Sandoz, a global leader in off-patent (generic and biosimilar) medicines, today announces further progress on its biosimilar pipeline, with the release of positive results from the integrated ROSALIA Phase I/III clinical trial study for its proposed biosimilar denosumab.

“Biosimilars have the opportunity to create a substantial positive impact on patient access and healthcare systems sustainability,” said Florian Bieber, Global Head of Development, Sandoz Biopharmaceuticals. “Therefore, this important milestone means that we are one step closer to giving individuals living with osteoporosis access to a more affordable, biosimilar version of this critical medicine, which may help to change the course of their disease.”

Denosumab is indicated for treating a variety of conditions, including osteoporosis in postmenopausal women, in men at increased risk of fractures, treatment-induced bone loss, prevention of skeletal related complications in cancer that has spread to the bone, and giant cell tumor of the bone^{2,3,4,5}.

The results from the integrated Phase I/III study confirm the biosimilar matches the reference medicine in terms of pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity in the respective indications; and contributes to demonstration of similarity, which is the basis for use in all indications.

Approximately 500 million men and women worldwide may be affected by osteoporosis¹, which causes 8.9 million fractures annually – or one fracture every three seconds¹. By 2050, hip fractures are projected to increase by 240% in women and 310% in men compared to 1990¹.

The results come soon after Sandoz confirmed acceptance of license applications for two other proposed biosimilars. In July 2022, the application for the first-of-a-kind multiple sclerosis proposed biosimilar natalizumab was accepted for review by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). In June 2022, the EMA and FDA accepted for review Sandoz applications for the high-concentration formulation 100 mg/mL (HCF) of its biosimilar adalimumab.

Sandoz biosimilars help patients, in areas including immunology, oncology, nephrology, supportive care and endocrinology, access critical and potentially life-changing medicines sustainably and affordably. Sandoz has a leading global portfolio with eight marketed biosimilars and a further 15-plus in various stages of development.



In ROSALIA, 527 postmenopausal women with osteoporosis were randomized to receive either biosimilar denosumab or the reference medicine for up to 78 weeks of treatment. Objectives were to demonstrate similar efficacy in terms of change in lumbar spine bone mineral density, as well as similar pharmacokinetics and pharmacodynamics. The global clinical program for biosimilar denosumab was developed in consultation with major regulatory agencies and the results from this clinical study are expected to support regulatory approval.

About denosumab

Denosumab is a human monoclonal antibody designed to bind to the RANKL protein, an activator of osteoclasts (cells involved in breaking down bone tissue)². By binding to and inhibiting RANKL, denosumab decreases the production and activity of osteoclasts, resulting in a reduction of bone loss, and subsequently the likelihood of fractures and other serious bone conditions².

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that, if approved, such generic or biosimilar products will be approved for all indications included in the reference product’s label. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; the particular prescribing preferences of physicians and patients; competition in general, including potential approval of additional generic or biosimilar versions of such products; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; litigation outcomes, including intellectual property disputes or other legal efforts to prevent or limit Sandoz from selling its products; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Sandoz

Sandoz, a Novartis division, is a global leader in generic pharmaceuticals and biosimilars. Our purpose is to pioneer access for patients by developing and commercializing novel, affordable approaches that address unmet medical needs. Our ambition is to be the world’s leading and most valued generics company. Our broad portfolio of high-quality medicines, covering all major therapeutic areas, accounted for 2022 sales of USD 9.2 billion.

Sandoz on social media:

LinkedIn: <https://www.linkedin.com/company/sandoz> (<https://www.linkedin.com/company/sandoz>)
Twitter: https://twitter.com/sandoz_global (https://twitter.com/sandoz_global)
Facebook: <https://www.facebook.com/sandozglobal/> (<https://www.facebook.com/sandozglobal/>)
Instagram: <https://www.instagram.com/sandozglobal> (<https://www.instagram.com/sandozglobal>)

CEO Richard Saynor on LinkedIn: <https://www.linkedin.com/in/richard-saynor/> (<https://www.linkedin.com/in/richard-saynor/>)

References

- 1. International Osteoporosis Foundation. Facts and Statistics. Available from: <https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures> (<https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures>) [Last accessed: August 2022].
- 2. Amgen Europe B.V. Xgeva[®] (Denosumab): Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/xgeva-epar-product-information_en.pdf (https://www.ema.europa.eu/en/documents/product-information/xgeva-epar-product-information_en.pdf) [Last accessed: August 2022].

3. Amgen Europe B.V. Prolia® (Denosumab): Summary of Product Characteristics. Available

from: <https://www.ema.europa.eu/en/medicines/human/EPAR/prolia>

 Sandoz | en ▼

(<https://www.ema.europa.eu/en/medicines/human/EPAR/prolia>) [Last accessed: August 2022].

4. Amgen Inc. Prolia® (Denosumab): Prescribing Information. Available

from: https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Prolia/prolia_pi.pdf

(https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Prolia/prolia_pi.pdf) [Last accessed: August 2022].

5. Amgen Inc. Xgeva® (Denosumab): Prescribing Information. Available

from: https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/xgeva/xgeva_pi.pdf

(https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/xgeva/xgeva_pi.pdf) [Last accessed: August 2022].

6. www.clinicaltrials.gov (<http://www.clinicaltrials.gov/>). Study Investigating PK, PD, Efficacy, Safety, and Immunogenicity of Biosimilar Denosumab (GP2411) in Patients with Postmenopausal Osteoporosis. NCT03974100. Available

from: <https://clinicaltrials.gov/ct2/show/NCT03974100?term=GP2411&rank=1> (<https://clinicaltrials.gov/ct2/show/NCT03974100?term=GP2411&rank=1>) [Last accessed: August 2022].

Sandoz and Novartis Global Communications

Sandoz Communications Global

Chris Lewis
+49 174 244 9501 (mobile)
chris.lewis@sandoz.com (<mailto:chris.lewis@sandoz.com>)

Sandoz US Communications

Leslie Pott
+1 201 354 0279 (mobile)
leslie.pott@sandoz.com (<mailto:leslie.pott@sandoz.com>)

Novartis Communications and Engagement

Richard Jarvis
+41 79 584 2326 (mobile)
richard.jarvis@novartis.com (<mailto:richard.jarvis@novartis.com>)

Novartis Media Relations

E-mail: media.relations@novartis.com (<mailto:media.relations@novartis.com>)

Novartis Investor Relations

Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com (<mailto:investor.relations@novartis.com>)

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 778 5052
Nicole Zinsli-Somm	+41 79 325 2084		
Isabella Zinck	+41 61 324 7188		

 Share

 Print (/node/52936/printable/print)

 Save (/node/52936/printable/pdf)

EXHIBIT 2



Novartis International AG
 Novartis Global
 Communications
 CH-4002 Basel
 Switzerland

<https://www.novartis.com>

CONDENSED INTERIM FINANCIAL REPORT – SUPPLEMENTARY DATA

Novartis Q3 and 9M 2019 Condensed Interim Financial Report – Supplementary Data

INDEX	Page
GROUP AND DIVISIONAL OPERATING PERFORMANCE Q3 and 9M 2019	
Group	2
Innovative Medicines	6
Sandoz	12
CASH FLOW AND GROUP BALANCE SHEET	14
INNOVATION REVIEW	17
CONDENSED INTERIM CONSOLIDATED FINANCIAL STATEMENTS	
Consolidated income statements	20
Consolidated statements of comprehensive income	22
Consolidated balance sheets	24
Consolidated statements of changes in equity	25
Consolidated statements of cash flows	28
Notes to condensed interim consolidated financial statements, including update on legal proceedings	30
SUPPLEMENTARY INFORMATION	56
CORE RESULTS	
Reconciliation from IFRS to core results	58
Group	60
Innovative Medicines	62
Sandoz	64
Corporate	66
Discontinued operations	68
ADDITIONAL INFORMATION	
Income from associated companies	70
Condensed consolidated changes in net debt / Share information	71
Free cash flow	72
Currency translation rates	74
DISCLAIMER	75

Novartis Q3 and 9M 2019 Condensed Interim Financial Report – Supplementary Data

Key figures ¹	Q3 2019 USD m	Q3 2018 USD m	% change USD cc ²		9M 2019 USD m	9M 2018 USD m	% change USD cc ²	
Net sales to third parties from continuing operations	12 172	11 016	10	13	35 042	33 270	5	9
Divisional operating income from continuing operations	2 595	2 542	2	5	7 823	7 666	2	9
Corporate income and expense, from continuing operations, net	- 237	- 303	22	21	- 560	- 625	10	8
Operating income from continuing operations	2 358	2 239	5	9	7 263	7 041	3	10
As % of net sales	19.4	20.3			20.7	21.2		
Income from associated companies	253	213	19	19	509	6 297	nm	nm
Interest expense	- 216	- 229	6	5	- 647	- 684	5	4
Other financial income and expense	12	28	- 57	- 33	56	108	- 48	- 37
Taxes	- 366	- 369	1	- 3	- 1 163	- 1 182	2	- 5
Net income from continuing operations	2 041	1 882	8	12	6 018	11 580	- 48	- 45
Net loss from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders		- 258	nm	nm	- 101	- 160	nm	nm
Gain on distribution of Alcon Inc. To Novartis AG shareholders					4 691		nm	nm
Net income	2 041	1 624	26	30	10 608	11 420	- 7	- 3
Basic earnings per share from continuing operations (USD)	0.90	0.81	11	14	2.62	4.99	- 47	-44
Basic earnings per share from discontinued operations (USD)		-0.11	nm	nm	2.00	-0.07	nm	nm
Basic earnings per share (USD)	0.90	0.70	29	32	4.62	4.92	- 6	-2
Cash flows from operating activities from continuing operations	4 562	3 720	23		10 007	9 613	4	
Free cash flow from continuing operations²	3 968	3 156	26		9 449	8 343	13	
Core²								
Core operating income from continuing operations	3 748	3 258	15	18	10 650	9 445	13	18
As % of net sales	30.8	29.6			30.4	28.4		
Core net income from continuing operations	3 212	2 820	14	17	9 119	8 239	11	16
Core net income from discontinued operations		244	nm	nm	278	818	nm	nm
Core net income	3 212	3 064	5	7	9 397	9 057	4	9
Core basic earnings per share from continuing operations (USD)	1.41	1.22	16	19	3.97	3.55	12	17
Core basic earnings per share from discontinued operations (USD)		0.10	nm	nm	0.12	0.35	nm	nm
Core basic earnings per share (USD)	1.41	1.32	7	9	4.09	3.90	5	10

nm = not meaningful

¹ Continuing operations include the businesses of Innovative Medicines and Sandoz divisions and Corporate activities and discontinued operations include the business of Alcon. See page 44 for full explanation

² Constant currencies (cc), core results and free cash flow are non-IFRS measures. An explanation of non-IFRS measures can be found on page 56. Unless otherwise noted, all growth rates in this release refer to same period in prior year.

Financials

In order to comply with International Financial Reporting Standards (IFRS), Novartis has separated the Group's reported financial data for the current and prior years into "continuing" and "discontinued" operations. The results of the Alcon business are reported as discontinued operations. See page 44 and Notes 2, 3 and 11 for a full explanation.

Novartis continues to expect the previously-announced divestment of the Sandoz US oral solids and dermatology portfolio to be completed in the coming months, pending regulatory approval. Novartis remains fully committed to this business until it is divested to Aurobindo. The results of this business are included in continuing operations.

The commentary below focuses on continuing operations including the businesses of Innovative Medicines and Sandoz (including the US generic oral solids and dermatology portfolio), as well as the continuing Corporate functions. We also provide information on discontinued operations.

Continuing operations third quarter

Net sales

Net sales were USD 12.2 billion (+10%, +13% cc) in the third quarter driven by volume growth of 16 percentage points (cc), mainly from *Cosentyx*, *Entresto*, *Zolgensma* and the *Xiidra* acquisition. Strong volume growth was partly offset by the negative impacts of pricing (-2 percentage points cc) and generic competition (-1 percentage point cc).

Corporate income and expense, net

Corporate income and expense, which includes the cost of Group headquarters and coordination functions, amounted to an expense of USD 237 million in the third quarter compared to USD 303 million in prior year, mainly on account of lower impairment charges from the Novartis Venture Fund financial assets.

Operating income

Operating income was USD 2.4 billion (+5%, +9% cc) mainly driven by higher sales and productivity, partly offset by growth investments, lower divestments and higher amortization. Operating income margin was 19.4% of net sales, decreasing by 0.9 percentage points (-0.7 percentage points cc). Core adjustments amounted to USD 1.4 billion (2018: USD 1.0 billion).

Core operating income was USD 3.7 billion (+15%, +18% cc) mainly driven by higher sales and productivity programs, partly offset by growth investments. Core operating income margin was 30.8% of net sales, increasing by 1.2 percentage points (+1.4 percentage points cc).

Income from associated companies

Income from associated companies increased to USD 253 million from USD 213 million in prior year due to a higher estimated income from Roche Holding AG.

Core income from associated companies increased to USD 313 million from USD 293 million in prior year due to a higher estimated core income contribution from Roche Holding AG.

Interest expense and other financial income/expense

Interest expense decreased to USD 216 million from USD 229 million in prior year, as the decrease in interest expense due to lower outstanding debts more than offset the additional interest expense on lease liabilities of USD 18 million, following the implementation of IFRS 16 Leases as of January 1, 2019.

Other financial income and expense amounted to an income of USD 12 million in the quarter compared to an income of USD 28 million in prior year, mainly due to lower interest income and higher currency losses.

Taxes

The tax rate in the third quarter was 15.2% compared to 16.4% in prior year. The decrease from prior year was mainly the result of a change in profit mix.

The core tax rate for continuing operations was 16.4% compared to 15.8% in prior year, mainly as a result of a change in profit mix.

Net income and EPS

Net income was USD 2.0 billion (+8%, +12% cc) driven by higher operating income and higher income from associated companies. EPS was USD 0.90 (+11%, +14% cc), growing faster than net income driven by lower weighted average number of shares outstanding.

Core net income was USD 3.2 billion (+14%, +17% cc) driven by growth in core operating income. Core EPS was USD 1.41 (+16%, +19% cc) growing faster than core net income driven by lower weighted average number of shares outstanding.

Free cash flow from continuing operations amounted to USD 4.0 billion (+26% USD) compared to USD 3.2 billion in prior year, mainly driven by higher net cash flows from operating activities.

Continuing operations nine months

Net sales

Net sales were USD 35.0 billion (+5%, +9% cc) in the first nine months driven by volume growth of 12 percentage points (cc), mainly from *Cosentyx*, *Entresto* and *Lutathera*. Strong volume growth was partly offset by the negative impacts of pricing (-2 percentage points cc) and generic competition (-1 percentage point cc).

Corporate income and expense, net

Corporate income and expense, which includes the cost of Group headquarters and coordination functions, amounted to an expense of USD 560 million in the nine months compared to USD 625 million in prior year mainly driven by lower impairment charges from the Novartis Venture Fund financial assets.

Operating income

Operating income was USD 7.3 billion (+3%, +10% cc) mainly driven by higher sales, improved gross margin and productivity programs, partly offset by growth investments, legal provisions and higher restructuring charges. Operating income margin was 20.7% of net sales, decreasing by 0.5 percentage points (+0.2 percentage points cc). Core adjustments amounted to USD 3.4 billion (2018: USD 2.4 billion).

Core operating income was USD 10.7 billion (13%, +18% cc) mainly driven by higher sales, improved gross margin and productivity programs, partly offset by growth investments. Core operating income margin was 30.4% of net sales, increasing by 2.0 percentage points (+2.4 percentage points cc).

Income from associated companies

Income from associated companies amounted to USD 509 million in the first nine months of 2019 compared to USD 6.3 billion in prior year. This decrease is mainly due to the pre-tax gain of USD 5.8 billion recognized on the divestment of the 36.5% stake in the GSK consumer healthcare joint venture in 2018.

The share of income from Roche was USD 510 million compared to USD 384 million in prior year. The estimated income for Roche Holding AG, net of amortization, was USD 596 million compared to USD 509 million in prior year and was partly offset by the negative prior year true up of USD 129 million in the first quarter of 2019, compared to a negative prior year true up of USD 125 million recognized in the first quarter of 2018. In addition, a USD 43 million income from revaluation of deferred tax liability, recognized upon initial accounting of the Roche investment, was recorded in the first quarter of 2019, following a change in the enacted tax rate in February 2019 of the Swiss Canton Basel-Stadt, effective January 1, 2019.

Core income from associated companies in the first nine months decreased to USD 844 million compared to USD 899 million in prior year due to the discontinuation of core income from the GSK consumer healthcare joint venture.

The core income contribution from Roche Holding AG increased to USD 845 million from USD 756 million in prior year. The increase is due to the recognition of a favorable prior year core income true up of USD 32 million compared to a favorable true up of USD 8 million in the first quarter of 2018, and to a higher estimated core income contribution from Roche for the current period.

Interest expense and other financial income/expense

Interest expense decreased to USD 647 million from USD 684 million in prior year, as the decrease in interest expense due to lower outstanding debts more than offset the additional interest expense on lease liabilities of USD 50 million, following the implementation of IFRS 16 Leases as of January 1, 2019.

Other financial income and expense amounted to an income of USD 56 million compared to USD 108 million in prior year, as higher currency losses were partly offset by higher interest income.

Taxes

The tax rate in the first nine months was 16.2% compared to 9.3% in prior year. In February 2019, the Swiss canton Basel-Stadt enacted a tax rate reduction effective January 1, 2019. In May 2019, Swiss federal tax reform was enacted, which eliminated certain tax privileges, effective January 1, 2020. This required a revaluation of certain deferred tax assets and liabilities to the newly enacted tax rates. The impact of this revaluation was offset by the impact of a change to uncertain tax positions. The prior year tax rate was significantly impacted by the divestment of the 36.5% stake in the GSK consumer healthcare joint venture.

Excluding the impacts of Swiss canton Basel-Stadt tax rate reduction, the Swiss federal tax reform and the changes to uncertain tax positions in the first half and the GSK consumer healthcare joint venture divestment in prior year, the tax rate in the first nine months would have been 15.4% compared to 16.2% in prior year. The decrease from prior year was mainly the result of a change in profit mix.

The core tax rate was 16.4% compared to 15.7% in prior year, mainly as a result of a change in profit mix.

Net income and EPS

Net income was USD 6.0 billion (-48%, -45% cc) as prior year benefited from a USD 5.7 billion net gain recognized from the sale of our stake in the GSK consumer healthcare joint venture. EPS was USD 2.62 (-47%, -44% cc) benefitting from lower weighted average number of shares outstanding.

Core net income was USD 9.1 billion (+11%, +16% cc) driven by growth in core operating income partly offset by the discontinuation of core income from the GSK consumer healthcare joint venture. Core EPS was USD 3.97 (+12%, +17% cc) growing faster than core net income driven by lower weighted average number of shares outstanding.

Free cash flow from continuing operations amounted to USD 9.4 billion (+13% USD) compared to USD 8.3 billion in prior year. The increase is mainly driven by higher operating income adjusted for non-cash items and higher real estate divestment proceeds, partly offset by higher working capital, which in prior year included the receipt of a GSK sales milestone from the divested Vaccines business of USD 0.4 billion, and lower dividends received from associated companies, as prior year included the GSK consumer healthcare joint venture which was divested in Q2 2018.

Discontinued operations

Discontinued operations include the business of Alcon and certain Corporate costs directly attributable to Alcon up to the spin-off date. As the Alcon spin-off was completed on April 9, 2019, there were no operating results in the third quarter of 2019.

Discontinued operations net sales in the first nine months of 2019 were USD 1.8 billion compared to USD 5.4 billion in 2018 and operating income amounted to USD 71 million compared to an operating loss of USD 171 million in 2018. Net income from discontinued operations in the first nine months of 2019 amounted to USD 4.6 billion compared to a net loss of USD 160 million in 2018 driven by the non-taxable non-cash net gain on distribution of Alcon Inc. to Novartis AG shareholders which amounted to USD 4.7 billion. For further details see Note 3 "Significant transactions – Completion of the spin-off of the Alcon business through a dividend in kind distribution to Novartis AG shareholders".

Total Group third quarter

For the total Group, net income amounted to USD 2.0 billion compared to USD 1.6 billion in prior year, and basic earnings per share was USD 0.90 compared to USD 0.70 in prior year. Cash flow from operating activities for the total Group amounted to USD 4.6 billion and free cash flow to USD 4.0 billion.

Total Group nine months

For the total Group, net income amounted to USD 10.6 billion compared to USD 11.4 billion in prior year, and basic earnings per share was USD 4.62 compared to USD 4.92 in prior year. Cash flow from operating activities for the total Group amounted to USD 10.1 billion and free cash flow to USD 9.4 billion.

Innovative Medicines

	Q3 2019 USD m	Q3 2018 USD m	% change USD cc		9M 2019 USD m	9M 2018 USD m	% change USD cc	
Net sales	9 688	8 596	13	15	27 794	25 870	7	11
Operating income	2 404	2 184	10	13	7 077	6 571	8	14
As % of net sales	24.8	25.4			25.5	25.4		
Core operating income	3 300	2 897	14	16	9 528	8 382	14	19
As % of net sales	34.1	33.7			34.3	32.4		

Third quarter**Net sales**

Net sales were USD 9.7 billion (+13%, +15% cc) in the third quarter. Pharmaceuticals BU sales grew 13% (+15% cc), driven by continuing momentum on *Cosentyx* and *Entresto* and the benefit from the first full quarter of sales from *Zolgensma* and *Xiidra*. Oncology BU grew 12% (+14% cc) driven by continuing momentum on *Promacta/Revolade*, *Tafinlar* + *Mekinist* and *Kisqali* and the benefit from launches including *Lutathera*, *Kymriah* and *Piqray*. Volume contributed 17 percentage points to sales growth. Generic competition had a negative impact of 1 percentage point. Net pricing had a negative impact of 1 percentage point.

Regionally, US sales (USD 3.7 billion, +24%) delivered a strong performance driven by *Zolgensma*, *Cosentyx*, *Xiidra*, *Entresto* and *Lutathera*. Europe sales (USD 3.2 billion, +6%, +10% cc) benefited from continued strong performance of *Entresto*, *Tafinlar* + *Mekinist*, *Xolair* and *Kymriah*. Japan sales were USD 0.6 billion (+8%, +4% cc). Emerging Growth Markets sales grew (+10%, +13% cc), led by strong double-digit growth in China.

Pharmaceuticals BU sales were USD 6.0 billion (+13%, +15% cc). *Cosentyx* (USD 937 million, +25%, +27% cc) grew double-digit across all indications. *Entresto* (USD 430 million, +59%, +61% cc) continued to deliver strong double-digit performance, benefiting from the PIONEER data on hospital initiation and higher demand in ambulatory settings. *Zolgensma* (USD 160 million) had a strong launch. *Lucentis* continued to grow (USD 500 million, +2%, +5% cc) while *Xolair* (USD 299 million, +17%, +22% cc) continued double-digit growth. *Gilenya* (USD 829 million, +1%, +3% cc) was broadly in line with prior year.

Oncology BU sales were USD 3.7 billion (+12%, +14% cc). Growth was mainly driven by *Promacta/Revolade* (USD 380 million, +29%, +31% cc), *Lutathera* (USD 119 million, +113%, +116% cc), *Kymriah* (USD 79 million, +295%, +295% cc), *Tafinlar* + *Mekinist* (USD 345 million, +19%, +22% cc), *Kisqali* (USD 123 million, +71%, +76% cc) and *Piqray* (USD 43 million) had a strong launch.

Operating income

Operating income was USD 2.4 billion (+10%, +13% cc) mainly driven by continued strong sales growth and productivity, partly offset by growth investments and lower divestment gains. Operating income margin was 24.8% of net sales decreasing 0.6 percentage points (-0.5 percentage points in cc).

Core adjustments were USD 0.9 billion, including USD 0.7 billion for amortization of intangible assets. Prior year core adjustments were USD 0.7 billion. Core adjustments increased compared to prior year mainly due to prior year divestment gains.

Core operating income was USD 3.3 billion (+14%, +16% cc) mainly driven by higher sales and productivity, partly offset by growth investments. Core operating income margin was 34.1% of net sales, increasing 0.4 percentage points (+0.4 percentage points cc). Core gross margin decreased by 0.3 percentage points (cc) as productivity improvements were more than offset by the ramp up of capacity for cell & gene therapy. Core R&D expenses as a percentage of net sales were in line with prior year. Core SG&A expenses declined by 0.7 percentage points (cc) mainly driven by productivity and sales leverage. Core Other Income and Expense did not have a material impact on margin.

Nine Months

Net sales

Net sales were USD 27.8 billion (+7%, +11% cc) in the first nine months. Pharmaceuticals BU grew 8% (+12% cc) driven by *Cosentyx* reaching USD 2.6 billion and *Entresto* USD 1.2 billion. Oncology BU grew 7% (+11% cc) driven by AAA including *Lutathera*, as well as *Promacta/Revolade*, *Tafinlar + Mekinist* and *Kisqali*. Volume contributed 13 percentage points to sales growth. Generic competition had a negative impact of 1 percentage point. Net pricing had a negative impact of 1 percentage point.

Regionally, US sales (USD 10.1 billion, +16%) delivered a strong performance driven by *Cosentyx*, *Entresto* and *Lutathera*. Europe sales (USD 9.5 billion, +3%, +10% cc) benefited from continued strong performance of *Entresto*, *Tafinlar + Mekinist*, *Jakavi*, *Cosentyx* and *Lucentis*. Japan sales were USD 1.8 billion (+3%, +2% cc). Emerging Growth Markets sales grew (+4%, +12% cc), led by double-digit growth in China.

Operating income

Operating income was USD 7.1 billion (+8%, +14% cc), mainly driven by continued strong sales growth and productivity, partly offset by growth investments and legal provisions. Operating income margin was 25.5% of net sales, increasing 0.1 percentage points (+0.7 percentage points cc).

Core adjustments were USD 2.5 billion, mainly due to USD 1.7 billion of amortization. Core adjustments increased compared to prior year mainly driven by higher legal provisions.

Core operating income was USD 9.5 billion (+14%, +19% cc) mainly driven by higher sales and productivity, partly offset by higher growth investments. Core operating income margin was 34.3% of net sales, increasing 1.9 percentage points (+2.2 percentage points cc). Core gross margin increased by 0.3 percentage points (cc), mainly driven by productivity. Core R&D expenses decreased by 1.0 percentage points (cc) mainly driven by sales leverage, productivity and portfolio prioritization. Core SG&A expenses declined by 0.6 percentage points (cc) mainly driven by sales leverage and productivity. Core Other Income and Expense, net increased the margin by 0.3 percentage points (cc).

ONCOLOGY BUSINESS UNIT

	Q3 2019	Q3 2018	% change		9M 2019	9M 2018	% change	
	USD m	USD m	USD	cc	USD m	USD m	USD	cc
<i>Tasigna</i>	487	444	10	11	1 389	1 398	-1	2
<i>Sandostatin</i>	388	389	0	1	1 183	1 188	0	2
<i>Afinitor/Votubia</i>	400	374	7	8	1 174	1 157	1	4
<i>Promacta/Revolade</i>	380	295	29	31	1 036	844	23	26
<i>Tafinlar + Mekinist¹</i>	345	291	19	22	982	842	17	22
<i>Gleevec/Glivec</i>	320	380	-16	-14	950	1 188	-20	-17
<i>Jakavi</i>	279	248	13	17	821	721	14	21
<i>Exjade/Jadenu</i>	253	263	-4	-2	744	813	-8	-6
<i>Votrient</i>	198	197	1	2	578	630	-8	-5
<i>Lutathera</i>	119	56	113	116	334	86	nm	nm
<i>Kisqali</i>	123	72	71	76	325	175	86	92
<i>Kymriah</i>	79	20	nm	nm	182	48	nm	nm
<i>Piqray</i>	43		nm	nm	49		nm	nm
Other	301	276	9	11	895	839	7	10
Total Oncology business unit	3 715	3 305	12	14	10 642	9 929	7	11

¹Majority of sales for *Mekinist* and *Tafinlar* are combination, but both can be used as a monotherapy
nm = not meaningful

Tasigna (USD 487 million, +10%, +11% cc) grew in the US and EGM, partially offset by a decline in Europe.

Sandostatin (USD 388 million, 0%, +1% cc) sales were broadly in line with prior year, as growth in the US was offset by competitive pressure, mainly in EGM and Japan.

Afinitor/Votubia (USD 400 million, +7%, +8% cc) showed solid growth in the US, partially offset by first generic competition in Europe. In the US, the Abbreviated New Drug Application (ANDA) challenges to the compound patent, and the ANDA and IPR challenges to the renal cell carcinoma use patent, have been resolved and the patents upheld. Novartis has resolved patent litigation with certain generic manufacturers which may result in limited generic competition for *Afinitor* toward the end of 2019, and additional generic competition starting in mid-2020.

Promacta/Revolade (USD 380 million, +29%, +31% cc) continued to grow at a strong double-digit rate across all regions driven by increased use in chronic immune thrombocytopenia (ITP) and further uptake as first-line treatment for severe aplastic anemia (SAA) in the US and Japan.

Tafinlar + Mekinist (USD 345 million, +19%, +22% cc) continued strong double-digit growth due to demand in metastatic and adjuvant melanoma as well as NSCLC, with ongoing uptake of the adjuvant melanoma indication in Europe.

Gleevec/Glivec (USD 320 million, -16%, -14% cc) continued to decline due to generic competition in most major markets.

Jakavi (USD 279 million, +13%, +17% cc) continued double-digit growth across all regions driven by demand in the myelofibrosis and polycythemia vera indications.

Exjade/Jadenu (USD 253 million, -4%, -2% cc) declined mainly due to pressure from generic competition in the US and in other regions.

Votrient (USD 198 million, +1%, +2% cc) sales were broadly in line with prior year.

Lutathera (USD 119 million, +113%, +116% cc) continued to grow led by the US, with over 160 centers actively treating patients, and ongoing launches in Europe. Sales from all AAA brands (including *Lutathera* and radiopharmaceutical diagnostic products) were USD 177 million.

Kisqali (USD 123 million, +71%, +76% cc) showed strong growth in the US driven by use in metastatic breast cancer patients, independent of menopausal status or combination partner, with solid uptake continuing in Europe and other regions.

Kymriah (USD 79 million) strong demand continued and sales increased primarily driven by ongoing uptake in the US and Europe. There are over 160 qualified treatment centers and more than 20 countries worldwide that have coverage for at least one indication. Reimbursement for DLBCL was received in Scotland and for both pediatric ALL and DLBCL in Italy.

Piqray (USD 43 million) US launch progressed well. *Piqray* is the first and only treatment for patients with a PIK3CA mutation in HR+/HER2- advanced breast cancer.

PHARMACEUTICAL BUSINESS UNIT

OPHTHALMOLOGY

	Q3 2019	Q3 2018	% change		9M 2019	9M 2018	% change	
	USD m	USD m	USD	cc	USD m	USD m	USD	cc
<i>Lucentis</i>	500	491	2	5	1 569	1 526	3	8
Travoprost Group	109	128	-15	-13	330	386	-15	-12
<i>Xiidra</i>	102		nm	nm	102		nm	nm
Other	503	475	6	7	1 548	1 519	2	5
Total Ophthalmology	1 214	1 094	11	13	3 549	3 431	3	8

nm = not meaningful

Lucentis (USD 500 million, +2%, +5% cc) grew driven by strong market growth.

Travoprost Group (USD 109 million, -15%, -13% cc) declined mainly due to increased competition in the US and generic competition in Europe.

Xiidra (USD 102 million) (lifitegrast) is a prescription eye drop solution approved to treat the signs and symptoms of dry eye disease. It is dosed twice per day, approximately 12 hours apart, in each eye. *Xiidra* is approved in multiple markets including the US, Canada and Australia. It is under regulatory review in a number of additional markets. Novartis acquired *Xiidra* from Takeda and began recording sales as of July 1, 2019. The integration is ongoing.

Luxturna is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. In January 2018, Spark Therapeutics entered into licensing and supply agreements with Novartis covering development, registration and commercialization rights to *Luxturna* in markets outside the US. In the UK, in September

2019 NICE recommended *Luxturna* for treating patients with vision loss due to RPE65 genetic mutations.

NEUROSCIENCE

	Q3 2019	Q3 2018	% change		9M 2019	9M 2018	% change	
	USD m	USD m	USD	cc	USD m	USD m	USD	cc
<i>Gilenya</i>	829	818	1	3	2 420	2 505	-3	0
<i>Zolgensma</i>	160		nm	nm	175		nm	nm
<i>Aimovig</i> ¹	33		nm	nm	75		nm	nm
<i>Mayzent</i>	4		nm	nm	9		nm	nm
Other	16	20	-20	-21	46	63	-27	-24
Total Neuroscience	1 042	838	24	26	2 725	2 568	6	9

nm = not meaningful

¹Ex-US, Ex-Japan sales are reported. *Aimovig* is co-commercialized with Amgen in the US, where Amgen records sales and Novartis has exclusive rights in all ex-US territories excluding Japan

Gilenya (USD 829 million, +1%, +3% cc) grew in the US benefitting from stock and trade movements, partly offset by increased competitive pressure worldwide. In the US, the ANDA (Abbreviated New Drug Application) proceedings challenging the compound patent and extensions expiring in 2019 have been resolved and the patent upheld.

Zolgensma (USD 160 million) was approved by the FDA on May 24, 2019 for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene. *Zolgensma* has been used to treat patients ranging in age from less than one month to two years old including all types of SMA. Novartis has been working closely with payers and to date plans are in place covering ~90% of commercial patients and ~30% of Medicaid patients. *Zolgensma* was filed in Europe with PRIME designation and in Japan with Sakigake designation in Q4 2018 for infant SMA. *Zolgensma* is currently under regulatory review in Europe with an anticipated CHMP decision in Q1 2020 and in Japan with anticipated decision in H1 2020. Novartis is fully committed to bringing this innovative therapy to European and Japanese patients in need as early as possible.

Aimovig (USD 33 million, ex-US) is the most prescribed anti-CGRP worldwide, with more than 300,000 patients prescribed worldwide in the post-trial setting. It has now been launched in 31 countries for the preventive treatment of migraine and additional launches are underway. *Aimovig* is co-commercialized with Amgen in the US, where Amgen records sales and Novartis has exclusive rights in all ex-US territories excluding Japan. The collaboration continues during the litigation between the companies and will remain in force until and unless a final court decision terminates the agreements.

Mayzent (USD 4 million) launch is progressing and efforts are ongoing to improve patient on-boarding which was slower due to the special needs of this population. *Mayzent* was approved by the FDA on March 26, 2019 and is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive MS, in adults. *Mayzent* is the only FDA approved oral therapy for active SPMS based on evidence from a pivotal prospective Phase III clinical trial (EXPAND) in a typical SPMS population.

IMMUNOLOGY, HEPATOLOGY and DERMATOLOGY

	Q3 2019	Q3 2018	% change		9M 2019	9M 2018	% change	
	USD m	USD m	USD	cc	USD m	USD m	USD	cc
<i>Cosentyx</i>	937	750	25	27	2 586	2 031	27	30
<i>Ilaris</i>	177	141	26	27	493	399	24	28
Total Immunology, Hepatology and Dermatology	1 114	891	25	27	3 079	2 430	27	30

Xolair sales for all indications are reported in the Respiratory franchise

Cosentyx (USD 937 million, +25%, +27% cc) continued momentum in the US (+31%) and in the rest of the world (+15%, +20% cc), driven by strong demand across indications and regions and strong first line access in all three indications. In September, Novartis announced positive new data from the Phase III PREVENT trial evaluating the efficacy and safety of *Cosentyx* in patients with non-radiographic axial spondyloarthritis (nr-axSpA). Nr-axSpA forms part of the axial spondyloarthritis (axSpA) spectrum and is characterized by chronic inflammatory back pain and symptoms such as nocturnal pain, fatigue, morning stiffness and functional disability. Novartis has submitted the data to EMA and plans to submit to the FDA. Nr-axSpA would be the fourth indication for *Cosentyx*.

Ilaris (USD 177 million, +26%, +27% cc) sales were driven by strong double-digit volume growth, mostly in Europe and the US.

Xolair continued to grow in Chronic Spontaneous Urticaria (CSU, also known as Chronic Idiopathic Urticaria, CIU), a severe skin disease. *Xolair* on a global level is managed by the Respiratory franchise which reports all *Xolair* sales.

RESPIRATORY

	Q3 2019 USD m	Q3 2018 USD m	% change USD cc		9M 2019 USD m	9M 2018 USD m	% change USD cc	
<i>Ultibro Breezhaler</i>	97	110	-12	-8	313	332	-6	0
<i>Seebri Breezhaler</i>	28	34	-18	-16	93	111	-16	-11
<i>Onbrez Breezhaler</i>	20	24	-17	-16	62	78	-21	-15
Subtotal COPD Portfolio	145	168	-14	-10	468	521	-10	-5
<i>Xolair</i>	299	255	17	22	870	771	13	20
Other	4	6	-33	-21	16	19	-16	-6
Total Respiratory	448	429	4	9	1 354	1 311	3	10

Xolair sales for all indications are reported in the Respiratory franchise

Xolair (USD 299 million, +17%, +22% cc) continued to grow in both indications Severe Allergic Asthma (SAA) and Chronic Spontaneous Urticaria (CSU). Growth was mainly driven by CSU indication and the recent approval of *Xolair* for home-use in Europe. We co-promote *Xolair* with Genentech in the US and share a portion of operating income, but we do not record any US sales.

Ultibro Breezhaler (USD 97 million, -12%, -8% cc) an inhaled LABA/LAMA, sales declined mainly due to enhanced competition in Japan and Europe.

Seebri Breezhaler (USD 28 million, -18%, -16% cc) an inhaled LAMA, and **Onbrez Breezhaler** (USD 20 million, -17%, -16% cc) an inhaled LABA, declined mainly due to competition in Europe.

CARDIOVASCULAR, RENAL AND METABOLISM

	Q3 2019 USD m	Q3 2018 USD m	% change USD cc		9M 2019 USD m	9M 2018 USD m	% change USD cc	
<i>Entresto</i>	430	271	59	61	1 208	710	70	75
Other	7	6	17	10	19	16	19	17
Total Cardiovascular, Renal & Metabolism	437	277	58	60	1 227	726	69	73

Entresto (USD 430 million, +59%, +61% cc) continued strong momentum fueled by increased demand in both hospital and ambulatory settings. *Entresto* further supported its benefit to patients as an essential treatment in Heart Failure with data presented at ESC from the PROVE and EVALUATE trials showing how *Entresto* works directly on the heart to reverse damage caused by Heart Failure. In the US, generic manufacturers have filed ANDAs challenging the Orange Book-listed patents.

ESTABLISHED MEDICINES

	Q3 2019 USD m	Q3 2018 USD m	% change USD cc		9M 2019 USD m	9M 2018 USD m	% change USD cc	
<i>Galvus Group</i>	320	307	4	5	955	957	0	5
<i>Diovan Group</i>	254	254	0	3	798	763	5	11
<i>Exforge Group</i>	249	253	-2	2	780	751	4	10
<i>Zortress/Certican</i>	122	120	2	5	362	344	5	10
<i>Neoral/Sandimmun(e)</i>	101	114	-11	-9	314	349	-10	-6
<i>Voltaren/Cataflam</i>	105	104	1	0	313	333	-6	-3
Other	567	610	-7	-5	1 696	1 978	-14	-10
Total Established Medicines	1 718	1 762	-2	0	5 218	5 475	-5	0

Galvus Group (USD 320 million, +4%, +5% cc) grew led by solid performance in Emerging Growth Markets, including China.

Diovan Group (USD 254 million, 0%, +3% cc) grew in Europe and Emerging Growth Markets, partially offset by declines in the US and Japan.

Exforge Group (USD 249 million, -2%, +2% cc) grew in Emerging Growth Markets, offset by decline in Europe and Japan due to generic competition.

Zortress/Certican (USD 122 million, +2%, +5% cc) continued to grow in most regions.

Neoral/Sandimmun(e) (USD 101 million, -11%, -9% cc) declined due to generic competition and mandatory price reductions.

Voltaren/Cataflam (USD 105 million, +1%, 0% cc) sales were broadly in line with prior year.

Sandoz

	Q3 2019	Q3 2018	% change		9M 2019	9M 2018	% change	
	USD m	USD m	USD	cc	USD m	USD m	USD	cc
Net sales	2 484	2 420	3	5	7 248	7 400	-2	2
Operating income	191	358	-47	-42	746	1 095	-32	-25
As % of net sales	7.7	14.8			10.3	14.8		
Core operating income	615	541	14	18	1 577	1 520	4	10
As % of net sales	24.8	22.4			21.8	20.5		

Sandoz US Generics Transaction

Novartis announced on September 6, 2018 that it has agreed to sell selected portions of its Sandoz US portfolio, specifically the Sandoz US dermatology business and US oral solids portfolio, to Aurobindo Pharma USA Inc. This transaction is expected to be completed in the coming months, pending regulatory approval. The results of this business are included in continuing operations.

Third quarter

Net sales

Net sales were USD 2.5 billion (+3%, +5% cc) driven by strong volume growth of 9 percentage points (cc) partially offset by 4 percentage points (cc) of price erosion mainly in the US. Excluding the US, net sales grew (+4%, +7% cc).

Sales in Europe were USD 1.3 billion (+8%, +12% cc) mainly driven by strong biosimilar growth. Sales in the US were USD 655 million declining 1% with the continued industry-wide pricing pressure mostly offset by first-to-market launches and Medicaid gross-to-net adjustments. Sales in Asia / Africa / Australasia were USD 333 million (-9%, -8% cc) impacted by high prior year base and market optimization. Sales in Canada and Latin America were USD 199 million (+5%, +7% cc).

Global sales of Biopharmaceuticals (biosimilars, biopharmaceutical contract manufacturing and *Glatopa*) grew to USD 430 million (+23%, +27% cc), driven by continued strong double-digit growth in Europe from *Hyrmoz* (adalimumab), *Rixathon* (rituximab), and *Erelzi* (etanercept). Launch roll-outs in Asia / Africa / Australasia continue to contribute to growth.

Retail sales were USD 1.9 billion (-1%, +1% cc) as sales from first-to-market launches offset pricing pressure. Total Anti-Infectives franchise sales were USD 321 million (-1%, +2% cc), including finished dosage forms sold under the Sandoz name and Anti-Infectives sold to third parties for sale under their own name (USD 124 million, +2%, +5% cc).

Operating income

Operating income was USD 191 million (-47%, -42% cc) impacted by changes in legal settlement provisions, higher net manufacturing and Sandoz transformation restructuring expenses and lower divestment income. Operating income margin was 7.7% of net sales, declining 7.1 percentage points (-6.6 percentage points cc).

Core adjustments were USD 424 million, including USD 79 million of amortization. Prior year core adjustments were USD 183 million. The change in core adjustments compared to prior year was driven by changes in legal settlement provisions and higher net manufacturing and Sandoz transformation restructuring expenses.

Core operating income was USD 615 million (+14%, +18% cc) driven by sales growth and continued gross margin improvements, including Medicaid gross-to-net adjustments. Core operating income margin was 24.8% of net sales, increasing 2.4 percentage points (2.8 percentage points cc). Core gross margin increased by 1.4 percentage points (cc), as favorable product and geographic mix, ongoing productivity improvements and Medicaid gross-to-net adjustments were partly offset by the impact of price erosion mainly in the US. Core R&D expenses decreased by 0.2 percentage points (cc) and Core SG&A expenses decreased by 0.5 percentage points (cc). Core Other Income and Expense increased the margin by 0.7 percentage points (cc) mainly due to lower net legal settlements partly offset by lower divestment income.

Nine months

Net sales

Net sales were USD 7.2 billion (-2%, +2% cc) driven by strong volume growth of 9 percentage points (cc) partially offset by 7 percentage points (cc) of price erosion, mainly in the US. Excluding the US, net sales grew (0%, +6% cc).

Sales in Europe were USD 3.8 billion (+2%, +9% cc) mainly driven by biosimilars. Sales in the US were USD 1.9 billion (-8%), mainly due to continued industry-wide pricing pressure. Sales in Asia / Africa / Australasia were USD 984 million (-4%, -1% cc) broadly in line with prior year. Sales in Canada and Latin America were USD 570 million (-1%, +5% cc).

Global sales of Biopharmaceuticals (biosimilars, biopharmaceutical contract manufacturing and *Glatopa*) grew to USD 1.2 billion (+13%, +18% cc), driven by continued strong double-digit growth in Europe from *Hyrimoz* (adalimumab), *Rixathon* (rituximab), and *Erelzi* (etanercept). Launch roll-outs in Asia / Africa / Australasia also contributed to growth.

Retail sales were USD 5.7 billion (-4%, 0% cc), as first-to-market launches slowed the decline in the US (-4%) and the segment grew in the rest of world. Total Anti-Infectives franchise sales were USD 970 million (-5%, -1% cc), including finished dosage forms sold under the Sandoz name and Anti-Infectives sold to third parties for sale under their own name (USD 383 million, -6%, -2% cc).

Operating income

Operating income was USD 746 million (-32%, -25% cc) impacted by changes in legal settlement provisions and higher net manufacturing and Sandoz transformation restructuring expenses. Operating income margin was 10.3% of net sales, declining 4.5 percentage points (-3.9 percentage points cc).

Core adjustments were USD 831 million, including USD 239 million of amortization. Prior year core adjustments were USD 425 million. The change in core adjustments compared to prior year was driven mainly by changes in legal settlement provisions, higher net manufacturing and Sandoz transformation restructuring expenses and lower gains from divestments.

Core operating income was USD 1.6 billion (+4%, +10% cc) as sales growth and gross margin improvements were partly offset by lower divestment income and higher net legal settlements. Core operating income margin was 21.8% of net sales, increasing 1.3 percentage points (1.6 percentage points cc). Core gross margin increased by 1.9 percentage points (cc), as favorable product and geographic mix and ongoing productivity improvements, were partly offset by the impact of price erosion mainly in the US. Core R&D expenses increased by 0.1 percentage points (cc) while core SG&A expenses decreased by 0.7 percentage points (cc) mainly driven by productivity and sales leverage. Core Other Income and Expense decreased the margin by 0.9 percentage points (cc) mainly due to lower divestment income and higher net legal settlements.

GROUP CASH FLOW AND BALANCE SHEET

Cash flow

Third quarter

Net cash flows from operating activities from continuing operations amounted to USD 4.6 billion, compared to USD 3.7 billion in the prior year quarter. The increase was mainly driven by higher net income adjusted for non-cash items and other adjustments, including divestment gains, and favorable working capital.

Net cash flows used in investing activities from continuing operations amounted to USD 3.4 billion, compared to USD 0.7 billion in the prior year quarter. The current year quarter includes mainly cash outflows for the purchase of property, plant and equipment of USD 0.4 billion, for intangible assets of USD 0.2 billion, for financial assets and other non-current assets of USD 0.1 billion and for acquisitions and divestments of businesses, net of USD 3.5 billion, mainly for the acquisition of *Xiidra* from Takeda Pharmaceutical Company Limited, partly offset by cash inflows from the proceeds of the sale of financial assets of USD 0.6 billion (including USD 543 million proceeds from the sale of Alcon Inc. shares) and intangible assets of USD 0.1 billion.

In the prior year quarter, net cash flows used in investing activities from continuing operations were mainly related to cash outflows for the purchase of property, plant and equipment of USD 0.3 billion, for intangible assets of USD 0.5 billion, and for financial and other non-current assets of USD 0.1 billion. This was partly offset by cash inflows from the sale of intangible and financial assets of USD 0.4 billion. Cash outflows for acquisitions of interests in associated companies, net amounted to USD 0.1 billion.

Net cash flows used in financing activities from continuing operations amounted to USD 2.7 billion, compared to USD 1.5 billion in the prior year quarter. The current year quarter mainly includes the cash outflows for net treasury share transactions of USD 2.9 billion (mainly related to the up to USD 5 billion share buyback), net payments of lease liabilities of USD 0.1 billion, partly offset by a net increase in financial debts of USD 0.3 billion.

In the prior year quarter, net cash flows used in financing activities from continuing operations included cash outflows for net treasury share transactions of USD 1.0 billion, net repayments of financial debts of USD 0.6 billion, partly offset by other net financing cash inflows of USD 0.2 billion.

Free cash flow from continuing operations amounted to USD 4.0 billion (+26% USD) compared to USD 3.2 billion in prior year quarter, mainly driven by higher net cash flows from operating activities.

Nine months

Net cash flows from operating activities from continuing operations amounted to USD 10.0 billion, compared to USD 9.6 billion in the prior year period. This increase was driven by higher net income adjusted for non-cash items and other adjustments, including divestment gains, partly offset by lower dividends received from associated companies due to the divestment of the GSK consumer healthcare joint venture in Q2 2018, higher provision payments and higher working capital, which included the receipt of a GSK sales milestone from the divested Vaccines business of USD 0.4 billion in the prior year period.

Net cash flows from operating activities from discontinued operations are USD 78 million, compared to USD 893 million in the prior year period. This reduction is due to the completion of the Alcon spin-off on April 9, 2019.

Net cash flows used in investing activities from continuing operations amounted to USD 1.4 billion, compared to USD 0.2 billion in the prior year period. The current year mainly includes cash outflows for the purchase of property, plant and equipment of USD 0.9 billion, for intangible assets of USD 0.7 billion, for financial assets and other non-current assets of USD 0.3 billion, and for acquisitions and divestments of businesses, net of USD 3.8 billion, mainly for the acquisition of IFM Tre, Inc. (USD 0.3 billion) and the acquisition of *Xiidra* from Takeda Pharmaceutical Company Limited (USD 3.5 billion), partly offset by net proceeds from the sales of marketable securities and commodities of USD 2.3 billion, cash inflows from the sale of property, plant and equipment of USD 0.8 billion (including the proceeds from the sale and leaseback of real estate), from the sale of financial assets of USD 0.7 billion (including USD 656 million proceeds from the sale of Alcon Inc. shares) and intangible assets of USD 0.4 billion.

In the prior year period, net cash flows used in investing activities from continuing operations were mainly related to the cash inflow of USD 13.0 billion from the divestment of our 36.5% stake in the GSK consumer healthcare joint venture. This was offset by cash outflows for the purchase of intangible assets of USD 1.2 billion and for the acquisitions and divestments of businesses, net of USD 11.9 billion, mainly Advanced Accelerator Applications S.A. of USD 3.5 billion, net (USD 3.9 billion, net of cash acquired USD 0.4 billion) and AveXis, Inc. of USD 8.3 billion, net (USD 8.7 billion, net of cash acquired USD 0.4 billion).

Net cash flows used in investing activities from discontinued operations amounted to USD 1.1 billion, compared to USD 0.5 billion in the prior year period. The current year period includes mainly the cash outflow for the acquisition of PowerVision, Inc. of USD 0.3 billion and USD 0.6 billion due to the derecognized cash and cash equivalents following the completion of the Alcon spin-off on April 9, 2019.

Net cash flows used in financing activities from continuing operations amounted to USD 15.7 billion, compared to USD 4.2 billion in the prior year period. The current year mainly includes the cash outflows for the dividend payment of USD 6.6 billion, for net treasury share transactions of USD 5.3 billion (mainly related to the up to USD 5 billion share buyback) and net cash outflows of USD 3.1 billion for non-current financial debts (mainly driven by the repayment at maturity of a US dollar bond of USD 3.0 billion). The net repayments of current financial debts amounted to USD 0.5 billion. Payments for lease liabilities, net and other financing cash flows resulted in a net cash outflow of USD 0.1 billion.

In the prior year period, net cash flows used in financing activities from continuing operations included cash outflows for the dividend payment of USD 7.0 billion, the repayment of non-current financial debts of USD 0.4 billion and for net treasury transactions of USD 1.4 billion. This was partly offset by cash inflows from the issuance of euro bonds totaling USD 2.8 billion (notional amount EUR 2.25 billion), the net increase in current financial debts of USD 1.2 billion, and other net financing cash inflows of USD 0.4 billion.

Net cash inflows from financing activities from discontinued operations amounted to USD 3.3 billion compared to a cash outflow of USD 0.5 billion in the prior year period. The current year period includes mainly the cash inflows of USD 3.5 billion from Alcon borrowings, partly offset by USD 0.2 billion payments for transaction costs.

Free cash flow from continuing operations amounted to USD 9.4 billion (+13% USD) compared to USD 8.3 billion in the prior year period. The increase is mainly driven by higher operating income adjusted for non-cash items and higher real estate divestment proceeds, partly offset by higher working capital, which in the prior year period included the receipt of a GSK sales milestone from the divested Vaccines business of USD 0.4 billion, and lower dividends received from associated companies, as the prior year period included the GSK consumer healthcare joint venture which was divested in Q2 2018.

Balance sheet

There has been a significant change in the consolidated balance sheet resulting from the spin-off of the Alcon business through the dividend in kind distribution to Novartis AG shareholders completed on April 9, 2019 (see Note 2, Note 3 and Note 11 for further details). The December 31, 2018 consolidated balance sheet includes the assets and liabilities of the Alcon business. The September 30, 2019 consolidated balance sheet excludes the assets and liabilities of the Alcon business, due to derecognition of the Alcon business at the date of the spin-off. The consolidated balance sheet discussion and analysis that follows excludes the impacts from derecognition of the Alcon business at the date of the spin-off.

Assets

Total non-current assets of USD 89.3 billion at September 30, 2019 increased by USD 3.0 billion compared to December 31, 2018, excluding the impact of the derecognition of the Alcon business non-current assets as a result of the spin-off. This increase was mainly driven by recognition of right-of-use assets resulting from the implementation of IFRS 16 – Leases on January 1, 2019 amounting to USD 1.7 billion, an increase in intangible assets other than goodwill of USD 1.7 billion, mainly from the acquisition of *Xiidra* from Takeda Pharmaceutical Company Limited, and the increase in financial assets of USD 0.8 billion, primarily from the financial investments in Alcon Inc. shares recognized by certain consolidated foundations through the Alcon spin-off. This was partially offset by the decrease in property, plant and equipment of USD 0.9 billion, mainly due to depreciation in excess of net additions and a decrease in goodwill of USD 0.1 billion, as additions were more than offset by currency translation

adjustments. Investments in associated companies, deferred tax assets and other non-current assets were broadly in line compared to December 31, 2018.

Total current assets of USD 26.7 billion at September 30, 2019 decreased by USD 5.5 billion compared to December 31, 2018, excluding the impact of the derecognition of the Alcon business current assets as a result of the spin-off. This decrease was mainly driven by the reduction in cash and cash equivalents of USD 4.7 billion and in marketable securities, commodities, time deposits and derivative financial instruments of USD 2.4 billion, mainly due to the repayment of financial debts and the dividend payment. This was partially offset by an increase in inventories by USD 0.6 billion, in trade receivables by USD 0.4 billion and in other current assets by USD 0.5 billion. Income tax receivable and assets of disposal group held for sale remained broadly in line compared to December 31, 2018.

Net assets of disposal group held for sale relate to the pending divestment of the Sandoz US dermatology business and generic US oral solids portfolio to Aurobindo Pharma USA Inc. announced on September 6, 2018, and amount to USD 0.8 billion (see Note 3). Novartis expects the divestment to be completed in the coming months, pending regulatory approval.

Liabilities

Total non-current liabilities of USD 35.2 billion increased by USD 0.4 billion compared to December 31, 2018, excluding the impact of the derecognition of the Alcon business non-current liabilities as a result of the spin-off. This increase was mainly driven by the recognition of lease liabilities resulting from the implementation of IFRS 16 – Leases on January 1, 2019 amounting to USD 1.7 billion, and the USD 1.2 billion increase in provisions and other non-current liabilities, mainly due to higher pension plan liabilities resulting from the decrease in discount rates used to calculate the actuarial defined benefit obligations. This was partially offset by the USD 2.3 billion decrease in long-term financial debts, mainly driven by the reclassification from non-current to current financial debt of USD 2.0 billion US dollar bonds due in 2020, and a USD 0.3 billion decrease in deferred tax liabilities.

Total current liabilities of USD 28.2 billion increased by USD 0.4 billion compared to December 31, 2018, excluding the impacts of the derecognition of the Alcon business current liabilities as a result of the spin-off. This was mainly driven by an increase in provisions and other current liabilities of USD 1.6 billion, primarily from higher legal and revenue deduction provisions, and increases in current income tax liabilities by USD 0.4 billion and in lease liabilities by USD 0.3 billion, resulting from the implementation of IFRS 16 – Leases on January 1, 2019. This was partially offset by a USD 1.6 billion decrease in financial debts and derivative financial instruments, mainly due to the repayment of USD 3.0 billion of bonds issued in February 2009, and a USD 0.2 billion decrease in trade payables.

Group equity

The Group's equity decreased by USD 26.1 billion to USD 52.6 billion at September 30, 2019 compared to USD 78.7 billion at December 31, 2018. This decrease was mainly due to derecognition of the dividend in kind distribution liability of USD 23.4 billion upon completion of the Alcon spin-off (see Note 2, 3 and 11 for further details), the cash-dividend payment of USD 6.6 billion, purchase of treasury shares of USD 5.5 billion, net actuarial losses of USD 1.3 billion, transaction costs of USD 0.3 billion, unfavorable currency translation differences of USD 0.5 billion and taxes on treasury shares of USD 0.2 billion. This was partially offset by net income of USD 10.6 billion, the net effect of exercise of options and employee transactions of USD 0.8 billion, and a decrease in the treasury share repurchase obligation under a share buyback trading plan of USD 0.3 billion.

Net debt and debt/equity ratio

The net debt increased to USD 19.4 billion at September 30, 2019 compared to USD 16.2 billion at December 31, 2018. The Group's liquidity amounted to USD 8.7 billion at September 30, 2019 compared to USD 16.0 billion at December 31, 2018, and the total of the non-current and current financial debt, including derivatives, amounted to USD 28.1 billion at September 30, 2019, compared to USD 32.1 billion at December 31, 2018. The debt/equity ratio increased to 0.54:1 at September 30, 2019 compared to 0.41:1 at December 31, 2018.

Innovation Review

Benefitting from our continued focus on innovation, Novartis has one of the industry's most competitive pipelines with more than 200 projects in clinical development.

Selected Innovative Medicines approvals: US, EU and Japan

Product	Active ingredient/ Descriptor	Indication	Approval date
<i>Lucentis</i>	ranibizumab	Retinopathy of prematurity	EU – Sep 2019
<i>Beovu</i> (RTH258)	brolocizumab	Neovascular (wet) AMD	US – Oct 2019

Selected Innovative Medicines projects awaiting regulatory decisions

Product	Indication	Completed submissions			News update
		US	EU	Japan	
<i>Cosentyx</i>	Non-radiographic axial spondyloarthritis		Q3 2019		- 52 week data for US submission positive in Q3. On track for filing to FDA in Q4
<i>Mayzent</i>	Secondary Progressive Multiple Sclerosis	Approved	Q3 2018	Q1 2019	- US approved in RMS including active SPMS
BYL719 (<i>Piqray</i> in US, alpelisib)	PIK3CA mutant HR+/HER2- postmenopausal advanced or metastatic BC	Approved	Q4 2018		
<i>Lucentis</i>	Retinopathy of prematurity		Approved	Q1 2019	
	Diabetic retinopathy		Q4 2018		- CHMP positive opinion received – Sep 2019
RTH258	Neovascular (wet) AMD	Approved	Q1 2019	Q2 2019	
SEG101	Sickle cell disease	Q2 2019	Q2 2019		- US Priority review
QMF149	Asthma		Q2 2019	Q3 2019	- QUARTZ study meets primary and key secondary endpoints - Positive results Phase III PALLADIUM study – Sep 2019
QVM149	Asthma		Q2 2019	Q3 2019	- Positive results Phase III IRIDIUM study – Sep 2019
<i>Xiidra</i>	Dry eye	Approved	Q4 2018		- CHMP opinion anticipated Q1 2020
<i>Xolair</i>	Nasal polyps	Q3 2019			
<i>Zolgensma</i> (AVXS-101)	Spinal Muscular Atrophy Type 1 (IV formulation)	Approved	Q4 2018	Q4 2018	

Selected Innovative Medicines pipeline projects

Project/ Compound	Potential indication/ Disease area	First planned submissions	Current Phase	News update
ABL001	Chronic myeloid leukemia 3 rd line	2021	III	
	Chronic myeloid leukemia 1 st line	≥2023	III	
ACZ885 (canakinumab)	Adjuvant NSCLC	2022	III	Enrollment ongoing for Phase III studies
	1 st line NSCLC	2021	III	
	2 nd line NSCLC	2021	III	
AVXS-101 IT	Spinal Muscular Atrophy Type 2/3 (IT formulation)	2020	I / II	- Interim data presented at AAN in May and updated at World Muscle Society in October - Awaiting FDA feedback on IT filing approach

AVXS-201	Rett Syndrome	≥2023	I	
BYL719 (Piqray in US)	PROS (PIK3CA-related overgrowth spectrum)	2020	II	
	HR- HER+ adv. breast cancer	≥2023	III	
	Triple negative breast cancer	≥2023	III	
	Head and neck squamous cell carcinoma	≥2023	III	
	Ovarian Cancer	≥2023	III	
CAD106	Alzheimer's disease	NA	II / III	- Program retired in Q3
CFZ533 (iscalimab)	Solid organ transplantation	≥2023	II	- Enrollment has started in the phase IIb de novo and maintenance kidney transplant study
	Sjogren's syndrome	≥2023	II	
Cosentyx	Non-radiographic axial spondyloarthritis	2019	US III	- Submitted to EMA in Q3, planned to submit to FDA in Q4
	Psoriatic arthritis head-to-head vs. adalimumab	2020	III	
	Ankylosing spondylitis head-to-head vs. adalimumab	2022	III	
	Hidradenitis suppurativa	2022	III	
	Giant cell arteritis	≥2023	II	
CSJ117	Severe asthma	≥2023	II	
ECF843	Dry eye	2022	II	
Entresto	Chronic heart failure with preserved ejection fraction	2019	III	- PARAGON-HF topline results presented at ESC – Sep 2019
	Post-acute myocardial infarction	2021	III	
HDM201	Acute myeloid leukemia	≥2023	II	
INC280 (capmatinib)	NSCLC (cMET amp and mut)	2019	II	- Primary analysis in the GEOMETRY mono -1 study demonstrates promising efficacy – June 2019
				- Breakthrough Therapy designation granted by FDA
				- Orphan Drug designation granted by FDA and MHLW (Japan)
Jakavi	Acute graft-versus-host disease (GvHD)	2021	III	
	Chronic graft-versus-host disease (GvHD)	2021	III	
KAE609 (cipargamin)	Malaria acute uncomplicated	≥2023	II	
	Severe Malaria	≥2023	II	
KAF156 (ganaplacide)	Malaria acute uncomplicated	≥2023	II	
Kisqali + endocrine therapy	HR+/HER2- early BC (adjuvant)	≥2023	III	- Enrollment ongoing
Kymriah (tisagenlecleucel) + pembrolizumab	r/r Follicular lymphoma	2021	II	
	r/r DLBCL in 1 st relapse	2021	III	
	r/r DLBCL	≥2023	I	
LAM320	Multi-drug resistant tuberculosis	2021	III	
LJC242 (tropifexor + cenicriviroc)	Non-alcoholic steatohepatitis (NASH)	≥2023	II	
LJN452 (tropifexor)	Non-alcoholic steatohepatitis (NASH)	≥2023	II	- FDA Fast Track designation

LMI070	Spinal Muscular Atrophy	≥2023	II	<ul style="list-style-type: none"> - FDA Orphan designation, EMA Orphan status obtained - Dose ranging study ongoing
LNP023	Paroxysmal nocturnal hemoglobinuria	2022	II	
	IgA nephropathy	≥2023	II	
	Membranous nephropathy	≥2023	II	
	C3 glomerulopathy	≥2023	II	
LOU064	Chronic spontaneous urticaria	≥2023	II	<ul style="list-style-type: none"> - Phase IIb study start achieved
¹⁷⁷ Lu-PSMA-617	Metastatic castration-resistant prostate cancer	2020	III	
LXE408	Visceral leishmaniasis	≥2023	I	
MBG453	Myelodysplastic syndrome	2021	II	
MOR106	Atopic dermatitis	≥2023	II	
OMB157 (ofatumumab)	Relapsing multiple sclerosis	2019	III	<ul style="list-style-type: none"> - Phase III ASCLEPIOS I & II studies met primary endpoints – Aug 2019
PDR001 + Tafinlar + Mekinist	Metastatic BRAF V600+ melanoma	2020	III	<ul style="list-style-type: none"> - On track for H2 2019 interim analysis data readout
PDR001 Combo	Metastatic melanoma	≥2023	II	<ul style="list-style-type: none"> - Enrollment ongoing
QAW039 (fevipiprant)	Asthma	2020	III	<ul style="list-style-type: none"> - ZEAL 1 and 2 missed primary endpoint - LUSTER 1 and 2 core registration trials on track for Q1 2020 readout
QBW251	COPD	≥2023	II	
QGE031 (ligelizumab)	Chronic spontaneous urticaria / chronic idiopathic urticaria	2021	III	<ul style="list-style-type: none"> - Phase III trials initiated enrollment
RTH258 (brolucizumab)	Diabetic macular edema	2021	III	
	Retinal vein occlusion	≥2023	III	
	Proliferative diabetic retinopathy	≥2023	III	
Rydapt (PKC412)	Acute myeloid leukemia (FLT3 wild type)	2022	III	
SAF312	Chronic ocular surface pain	≥2023	II	
TQJ230	Secondary prevention of cardiovascular events in patients with elevated levels of lipoprotein (a)	≥2023	III	<ul style="list-style-type: none"> - Phase III planned to initiate in Q1 of 2020
UNR844	Presbyopia	≥2023	II	
VAY736 (lanalumab)	Auto-immune hepatitis	≥2023	II	
	Primary Sjogren's syndrome	≥2023	II	<ul style="list-style-type: none"> - FDA Fast Track designation - Phase II study fully recruited
VAY785 (emricasan)	Non-alcoholic steatohepatitis (NASH)	NA	II	<ul style="list-style-type: none"> - Program retired in Q3
VPM087	1st line colorectal cancer / 1st line renal cell carcinoma	≥2023	I	
Xolair	Nasal polyps	2019	EU III	<ul style="list-style-type: none"> - POLYP 1 and POLYP2 positive study read out – May 2019
ZPL389 (adrioforant)	Atopic dermatitis	2022	II	<ul style="list-style-type: none"> - Phase IIb trial enrollment initiated

Selected Sandoz approvals and pipeline projects (biosimilars)

Project/Compound	Potential indication/ Disease area	Submission status	Current Phase	News update
LA-EP2006 (pegfilgrastim)	Chemotherapy-induced neutropenia and others (same as originator)	US EU	Submitted Approved	<ul style="list-style-type: none"> - Resubmitted to FDA in April
GP2411 (denosumab)	Osteoporosis, skeletal-related in bone met. pts (same as originator)	EU/US	III	<ul style="list-style-type: none"> - First patient enrolled July 2019

CONDENSED CONSOLIDATED FINANCIAL STATEMENTS

Consolidated income statements

Third quarter (unaudited)

(USD millions unless indicated otherwise)	Note	Q3 2019	Q3 2018	Change
Net sales to third parties from continuing operations	10	12 172	11 016	1 156
Sales to discontinued operations			28	-28
Net sales from continuing operations		12 172	11 044	1 128
Other revenues	10	310	342	-32
Cost of goods sold		-3 776	-3 463	-313
Gross profit from continuing operations		8 706	7 923	783
Selling, general and administration		-3 549	-3 261	-288
Research and development		-2 199	-2 147	-52
Other income		196	596	-400
Other expense		-796	-872	76
Operating income from continuing operations		2 358	2 239	119
Income from associated companies		253	213	40
Interest expense		-216	-229	13
Other financial income and expense		12	28	-16
Income before taxes from continuing operations		2 407	2 251	156
Taxes		-366	-369	3
Net income from continuing operations		2 041	1 882	159
Net loss from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders	11		-258	258
Net loss from discontinued operations			-258	258
Net income		2 041	1 624	417
<i>Attributable to:</i>				
Shareholders of Novartis AG		2 042	1 623	419
Non-controlling interests		-1	1	-2
Weighted average number of shares outstanding –				
Basic (million)		2 272	2 315	-43
<i>Basic earnings per share from continuing operations (USD) ¹</i>		<i>0.90</i>	<i>0.81</i>	<i>0.09</i>
<i>Basic earnings per share from discontinued operations (USD) ¹</i>			<i>-0.11</i>	<i>0.11</i>
Total basic earnings per share (USD) ¹		0.90	0.70	0.20
Weighted average number of shares outstanding –				
Diluted (million)		2 297	2 338	-41
<i>Diluted earnings per share from continuing operations (USD) ¹</i>		<i>0.89</i>	<i>0.80</i>	<i>0.08</i>
<i>Diluted earnings per share from discontinued operations (USD) ¹</i>			<i>-0.11</i>	<i>0.11</i>
Total diluted earnings per share (USD) ¹		0.89	0.69	0.19

¹ Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

Consolidated income statements

Nine months to September 30 (unaudited)

(USD millions unless indicated otherwise)	Note	9M 2019	9M 2018	Change
Net sales to third parties from continuing operations	10	35 042	33 270	1 772
Sales to discontinued operations		53	61	-8
Net sales from continuing operations		35 095	33 331	1 764
Other revenues	10	866	871	-5
Cost of goods sold		-10 433	-10 472	39
Gross profit from continuing operations		25 528	23 730	1 798
Selling, general and administration		-10 464	-10 040	-424
Research and development		-6 549	-6 255	-294
Other income		1 388	1 465	-77
Other expense		-2 640	-1 859	-781
Operating income from continuing operations		7 263	7 041	222
Income from associated companies		509	6 297	-5 788
Interest expense		-647	-684	37
Other financial income and expense		56	108	-52
Income before taxes from continuing operations		7 181	12 762	-5 581
Taxes		-1 163	-1 182	19
Net income from continuing operations		6 018	11 580	-5 562
Net loss from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders	11	-101	-160	59
Gain on distribution of Alcon Inc. to Novartis AG shareholders	3, 11	4 691		4 691
Net income/loss from discontinued operations		4 590	-160	4 750
Net income		10 608	11 420	-812
<i>Attributable to:</i>				
Shareholders of Novartis AG		10 607	11 416	-809
Non-controlling interests		1	4	-3
Weighted average number of shares outstanding –				
Basic (million)		2 298	2 322	-24
<i>Basic earnings per share from continuing operations (USD) ¹</i>		<i>2.62</i>	<i>4.99</i>	<i>-2.37</i>
<i>Basic earnings per share from discontinued operations (USD) ¹</i>		<i>2.00</i>	<i>-0.07</i>	<i>2.07</i>
Total basic earnings per share (USD) ¹		4.62	4.92	-0.30
Weighted average number of shares outstanding –				
Diluted (million)		2 323	2 345	-22
<i>Diluted earnings per share from continuing operations (USD) ¹</i>		<i>2.59</i>	<i>4.94</i>	<i>-2.35</i>
<i>Diluted earnings per share from discontinued operations (USD) ¹</i>		<i>1.98</i>	<i>-0.07</i>	<i>2.04</i>
Total diluted earnings per share (USD) ¹		4.57	4.87	-0.30

¹ Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

Consolidated statements of comprehensive income

Third quarter (unaudited)

(USD millions)	Q3 2019	Q3 2018	Change
Net income	2 041	1 624	417
<i>Other comprehensive income to be eventually recycled into the consolidated income statement:</i>			
Novartis share of other comprehensive income recognized by associated companies, net of taxes	-40	46	-86
Net investment hedge	81	1	80
Currency translation effects	-700	361	-1 061
Total of items to eventually recycle	-659	408	-1 067
<i>Other comprehensive income never to be recycled into the consolidated income statement:</i>			
Actuarial (losses)/gains from defined benefit plans, net of taxes	-418	350	-768
Fair value adjustments on equity securities, net of taxes	-99	52	-151
Total of items never to be recycled	-517	402	-919
Total comprehensive income	865	2 434	-1 569
<i>Attributable to:</i>			
Shareholders of Novartis AG	868	2 435	-1 567
Continuing operations	868	2 714	-1 846
Discontinued operations		-279	279
Non-controlling interests	-3	-1	-2

Consolidated statements of comprehensive income

Nine months to September 30 (unaudited)

(USD millions)	9M 2019	9M 2018	Change
Net income	10 608	11 420	-812
<i>Other comprehensive income to be eventually recycled into the consolidated income statement:</i>			
Fair value adjustments on debt securities, net of taxes	1	-2	3
Fair value adjustments on deferred cash flow hedges, net of taxes	1	9	-8
Total fair value adjustments on financial instruments, net of taxes	2	7	-5
Novartis share of other comprehensive income recognized by associated companies, net of taxes ¹	-94	-482	388
Net investment hedge	93	60	33
Currency translation effects ²	-511	594	-1 105
Total of items to eventually recycle	-510	179	-689
<i>Other comprehensive income never to be recycled into the consolidated income statement:</i>			
Actuarial (losses)/gains from defined benefit plans, net of taxes ³	-1 308	574	-1 882
Fair value adjustments on equity securities, net of taxes	-25	202	-227
Total of items never to be recycled	-1 333	776	-2 109
Total comprehensive income	8 765	12 375	-3 610
<i>Attributable to:</i>			
Shareholders of Novartis AG	8 766	12 376	-3 610
Continuing operations	4 189	12 500	-8 311
Discontinued operations	4 577	-124	4 701
Non-controlling interests	-1	-1	0

¹ In 2018, Novartis share of other comprehensive income recognized by associated companies, net of taxes of USD 511 million was recycled into the consolidated income statement as a result of the divestment of the investment in GSK Consumer Healthcare Holdings Ltd. (see Note 3).

² In 2019, cumulative currency translation gains of USD 123 million were recycled into the consolidated income statement as a result of the Alcon spin-off (see Note 3 and 11). In 2018, cumulative currency translation losses of USD 946 million were recycled into the consolidated income statement as a result of the divestment of the investment in GSK Consumer Healthcare Holdings Ltd.

³ Included in 2019 is a USD -358 million impact related to the revaluation of deferred tax assets on Swiss pension plans that were previously recognized through other comprehensive income. This revaluation resulted from enactment of the Swiss canton Basel-Stadt tax rate reduction, effective on January 1, 2019.

Consolidated balance sheets

(USD millions)	Note	Sep 30, 2019 (unaudited)	Dec 31, 2018 (audited)	Change
Assets				
Non-current assets				
Property, plant and equipment	10	11 878	15 696	-3 818
Right-of-use assets	6	1 682		1 682
Goodwill	10	26 306	35 294	-8 988
Intangible assets other than goodwill	10	29 694	38 719	-9 025
Investments in associated companies		8 284	8 352	-68
Deferred tax assets		7 985	8 699	-714
Financial assets		2 778	2 345	433
Other non-current assets		689	895	-206
Total non-current assets		89 296	110 000	-20 704
Current assets				
Inventories		6 123	6 956	-833
Trade receivables		7 826	8 727	-901
Income tax receivables		244	248	-4
Marketable securities, commodities, time deposits and derivative financial instruments		339	2 693	-2 354
Cash and cash equivalents		8 378	13 271	-4 893
Other current assets		2 920	2 861	59
Assets of disposal group held for sale	3	845	807	38
Total current assets		26 675	35 563	-8 888
Total assets		115 971	145 563	-29 592
Equity and liabilities				
Equity				
Share capital		936	944	-8
Treasury shares		-80	-69	-11
Reserves		51 668	77 739	-26 071
Issued share capital and reserves attributable to Novartis AG shareholders		52 524	78 614	-26 090
Non-controlling interests		74	78	-4
Total equity		52 598	78 692	-26 094
Liabilities				
Non-current liabilities				
Financial debts		20 131	22 470	-2 339
Lease liabilities	6	1 702		1 702
Deferred tax liabilities		5 682	7 475	-1 793
Provisions and other non-current liabilities		7 638	7 319	319
Total non-current liabilities		35 153	37 264	-2 111
Current liabilities				
Trade payables		4 669	5 556	-887
Financial debts and derivative financial instruments		8 017	9 678	-1 661
Lease liabilities	6	266		266
Current income tax liabilities		2 325	2 038	287
Provisions and other current liabilities		12 919	12 284	635
Liabilities of disposal group held for sale	3	24	51	-27
Total current liabilities		28 220	29 607	-1 387
Total liabilities		63 373	66 871	-3 498
Total equity and liabilities		115 971	145 563	-29 592

Consolidated statements of changes in equity

Third quarter (unaudited)

(USD millions)	Share capital	Treasury shares	Retained earnings	Total value adjustments	Issued share capital and reserves attributable to Novartis shareholders	Non-controlling interests	Total equity
Total equity at July 1, 2019	936	-67	55 645	-5 088	51 426	78	51 504
Net income			2 042		2 042	-1	2 041
Other comprehensive income			-40	-1 134	-1 174	-2	-1 176
Total comprehensive income			2 002	-1 134	868	-3	865
Purchase of treasury shares		-14	-2 521		-2 535		-2 535
Equity-based compensation		1	193		194		194
Taxes on treasury share transactions			-4		-4		-4
Decrease of treasury share repurchase obligation under a share buyback trading plan			2 573		2 573		2 573
Changes in non-controlling interests						-1	-1
Fair value adjustments on financial assets sold			38	-38			
Other movements ¹			2		2		2
Total of other equity movements		-13	281	-38	230	-1	229
Total equity at September 30, 2019	936	-80	57 928	-6 260	52 524	74	52 598

¹ Impact of hyperinflationary economies

(USD millions)	Share capital	Treasury shares	Retained earnings	Total value adjustments	Issued share capital and reserves attributable to Novartis shareholders	Non-controlling interests	Total equity
Total equity at July 1, 2018	944	-63	79 793	-3 859	76 815	86	76 901
Net income			1 623		1 623	1	1 624
Other comprehensive income			46	766	812	-2	810
Total comprehensive income			1 669	766	2 435	-1	2 434
Purchase of treasury shares		-6	-985		-991		-991
Exercise of options and employee transactions			1		1		1
Equity-based compensation			199		199		199
Increase of treasury share repurchase obligation under a share buyback trading plan			-526		-526		-526
Transaction costs ¹			-28		-28		-28
Changes in non-controlling interests						-1	-1
Fair value adjustments on financial assets sold			-1	1			
Impact of change in ownership of consolidated entities			4		4	-3	1
Other movements ²			29		29		29
Total of other equity movements		-6	-1 307	1	-1 312	-4	-1 316
Total equity at September 30, 2018	944	-69	80 155	-3 092	77 938	81	78 019

¹ Transaction costs directly attributable to the distribution (spin-off) of the Alcon business to Novartis AG shareholders (see Note 2)

² Impact of hyperinflationary economies

Consolidated statements of changes in equity

Nine months to September 30, 2019 (unaudited)

(USD millions)	Share capital	Treasury shares	Retained earnings	Total value adjustments	Issued share capital and reserves attributable to Novartis shareholders	Non-controlling interests	Total equity
Total equity at January 1, 2019, as previously reported	944	-69	82 191	-4 452	78 614	78	78 692
Impact of change in accounting policies ¹			3		3		3
Restated equity at January 1, 2019	944	-69	82 194	-4 452	78 617	78	78 695
Net income			10 607		10 607	1	10 608
Other comprehensive income			-94	-1 747	-1 841	-2	-1 843
Total comprehensive income			10 513	-1 747	8 766	-1	8 765
Dividends			-6 645		-6 645		-6 645
Dividend in kind ²			-23 434		-23 434		-23 434
Purchase of treasury shares		-31	-5 476		-5 507		-5 507
Reduction of share capital	-8	12	-4				
Exercise of options and employee transactions		3	197		200		200
Equity-based compensation		5	636		641		641
Shares delivered to Alcon employees as a result of the Alcon spin-off			32		32		32
Taxes on treasury share transactions ³			-189		-189		-189
Decrease of treasury share repurchase obligation under a share buyback trading plan			284		284		284
Transaction costs ⁴			-253		-253		-253
Changes in non-controlling interests						-1	-1
Fair value adjustments on financial assets sold			57	-57			
Fair value adjustments related to divestments			4	-4			
Impact of change in ownership of consolidated entities			-3		-3	-2	-5
Other movements ⁵			15		15		15
Total of other equity movements	-8	-11	-34 779	-61	-34 859	-3	-34 862
Total equity at September 30, 2019	936	-80	57 928	-6 260	52 524	74	52 598

¹ The impact of change in accounting policy includes USD 3 million related to the implementation of IFRS 16 – Leases (see Notes 2 and 6 for further details).

² Fair value of the dividend-in-kind of the Alcon business distributed to Novartis AG shareholders and ADR (American Depositary Receipt) holders approved at the 2019 Annual General Meeting held on February 28, 2019. Distribution was effected on April 9, 2019, whereby each Novartis AG shareholders and ADR holder received 1 Alcon Inc. share for every 5 Novartis AG shares/ADRs they held on April 8, 2019, close of business (see Note 2, 3 and 11 for further details).

³ In 2019, USD 69 million impact related to the revaluation of deferred tax liability on treasury shares are recognized through retained earnings. This revaluation resulted from the Swiss Federal tax reform enacted in May 2019, effective January 1, 2020.

⁴ Transaction costs directly attributable to the distribution (spin-off) of the Alcon business to Novartis AG shareholders (see Note 2)

⁵ Impact of hyperinflationary economies

Consolidated statements of changes in equity

Nine months to September 30, 2018 (unaudited)

(USD millions)	Share capital	Treasury shares	Retained earnings	Total value adjustments	Issued share capital and reserves attributable to Novartis shareholders	Non-controlling interests	Total equity
Total equity at January 1, 2018, as previously reported	969	-100	77 639	-4 340	74 168	59	74 227
Impact of change in accounting policies ¹			237	-177	60		60
Restated equity at January 1, 2018	969	-100	77 876	-4 517	74 228	59	74 287
Net income			11 416		11 416	4	11 420
Other comprehensive income			-482	1 442	960	-5	955
Total comprehensive income			10 934	1 442	12 376	-1	12 375
Dividends			-6 966		-6 966		-6 966
Purchase of treasury shares		-11	-1 780		-1 791		-1 791
Reduction of share capital	-25	34	-9				
Exercise of options and employee transactions		4	430		434		434
Equity-based compensation		4	551		555		555
Increase of treasury share repurchase obligation under a share buyback trading plan			-889		-889		-889
Transaction costs ²			-39		-39		-39
Changes in non-controlling interests						-1	-1
Fair value adjustments on financial assets sold			17	-17			
Impact of change in ownership of consolidated entities			1		1	24	25
Other movements ³			29		29		29
Total of other equity movements	-25	31	-8 655	-17	-8 666	23	-8 643
Total equity at September 30, 2018	944	-69	80 155	-3 092	77 938	81	78 019

¹ The impact of change in accounting policies includes USD 60 million relating to IFRS 15 implementation and USD 177 million relating to IFRS 9 implementation (see Note 1 and 29 of the 2018 Annual report).

² Transaction costs directly attributable to the distribution (spin-off) of the Alcon business to Novartis AG shareholders (see Note 2).

³ Impact of hyperinflationary economies

Consolidated statements of cash flows

Third quarter (unaudited)

(USD millions)	Note	Q3 2019	Q3 2018	Change
Net income from continuing operations		2 041	1 882	159
<i>Adjustments to reconcile net income from continuing operations to net cash flows from operating activities from continuing operations</i>				
Reversal of non-cash items and other adjustments	7	2 271	1 758	513
Dividends received from associated companies and others		0	1	-1
Interest received		32	68	-36
Interest paid		-134	-173	39
Other financial receipts		51	108	-57
Other financial payments		-9	-8	-1
Taxes paid ¹		-235	-219	-16
Net cash flows from operating activities from continuing operations before working capital and provision changes		4 017	3 417	600
Payments out of provisions and other net cash movements in non-current liabilities		-146	-208	62
Change in net current assets and other operating cash flow items		691	511	180
Net cash flows from operating activities from continuing operations		4 562	3 720	842
Net cash flows from operating activities from discontinued operations ¹			330	-330
Total net cash flows from operating activities		4 562	4 050	512
Purchase of property, plant and equipment		-357	-295	-62
Proceeds from sales of property, plant and equipment		-3	4	-7
Purchase of intangible assets		-205	-546	341
Proceeds from sales of intangible assets		140	286	-146
Purchase of financial assets		-69	-77	8
Proceeds from sales of financial assets		565	74	491
Purchase of other non-current assets		-10	-13	3
Proceeds from sales of other non-current assets		1	3	-2
Acquisitions of interests in associated companies, net ¹		-1	-81	80
Acquisitions and divestments of businesses, net	7	-3 460	-20	-3 440
Purchase of marketable securities and commodities		-69	-79	10
Proceeds from sales of marketable securities and commodities		67	43	24
Net cash flows used in investing activities from continuing operations		-3 401	-701	-2 700
Net cash flows from/used in investing activities from discontinued operations ²		3	-185	188
Total net cash flows used in investing activities		-3 398	-886	-2 512
Acquisition of treasury shares		-2 940	-1 013	-1 927
Proceeds from exercise of options and other treasury share transactions		5	1	4
Increase in non-current financial debts		93	0	93
Repayments of non-current financial debts		-186	-1	-185
Change in current financial debts		423	-603	1 026
Payments of lease liabilities, net		-92		-92
Receipts from finance sublease receivables		7		7
Impact of change in ownership of consolidated entities		-1	-7	6
Dividends paid to non-controlling interests and other financing cash flows		-2	157	-159
Net cash flows used in financing activities from continuing operations		-2 693	-1 466	-1 227
Net cash flows used in financing activities from discontinued operations ³		-20	-155	135
Total net cash flows used in financing activities		-2 713	-1 621	-1 092
Net change in cash and cash equivalents before effect of exchange rate changes		-1 549	1 543	-3 092
Effect of exchange rate changes on cash and cash equivalents		-64	11	-75
Total net change in cash and cash equivalents		-1 613	1 554	-3 167
Cash and cash equivalents at July 1		9 991	12 446	-2 455
Cash and cash equivalents at September 30		8 378	14 000	-5 622

¹ In Q3 2018, the total net tax payment amounted to USD 336 million, of which USD 75 million was included in the line "Acquisitions of interests in associated companies, net" and USD 42 million was included in the line "Net cash flows from operating activities from discontinued operations."

² For additional information related to Q3 2019 "Net cash flows from/used in investing activities from discontinued operations", refer to Note 11.

³ Including USD 20 million (Q3 2018: USD 33 million) transaction cost payments directly attributable to the distribution (spin-off) of the Alcon business to Novartis shareholders (see Note 2)

Consolidated statements of cash flows

Nine months to September 30 (unaudited)

(USD millions)	Note	9M 2019	9M 2018	Change
Net income from continuing operations		6 018	11 580	-5 562
<i>Adjustments to reconcile net income from continuing operations to net cash flows from operating activities from continuing operations</i>				
Reversal of non-cash items and other adjustments	7	6 372	-861	7 233
Dividends received from associated companies and others		463	719	-256
Interest received		172	154	18
Interest paid		-540	-545	5
Other financial receipts		61	146	-85
Other financial payments		-25	-22	-3
Taxes paid ¹		-1 195	-1 109	-86
Net cash flows from operating activities before working capital and provision changes from continuing operations		11 326	10 062	1 264
Payments out of provisions and other net cash movements in non-current liabilities		-662	-472	-190
Change in net current assets and other operating cash flow items		-657	23	-680
Net cash flows from operating activities from continuing operations		10 007	9 613	394
Net cash flows from operating activities from discontinued operations ¹		78	893	-815
Total net cash flows from operating activities		10 085	10 506	-421
Purchase of property, plant and equipment		-918	-810	-108
Proceeds from sales of property, plant and equipment		809	55	754
Purchase of intangible assets		-703	-1 188	485
Proceeds from sales of intangible assets		421	702	-281
Purchase of financial assets		-223	-148	-75
Proceeds from sales of financial assets		742	138	604
Purchase of other non-current assets		-34	-26	-8
Proceeds from sales of other non-current assets		4	7	-3
Acquisitions and divestments of interests in associated companies, net ¹		-4	12 919	-12 923
Acquisitions and divestments of businesses, net	7	-3 842	-11 879	8 037
Purchase of marketable securities and commodities		-189	-302	113
Proceeds from sales of marketable securities and commodities		2 495	334	2 161
Net cash flows used in investing activities from continuing operations		-1 442	-198	-1 244
Net cash flows used in investing activities from discontinued operations ²		-1 102	-458	-644
Total net cash flows used in investing activities		-2 544	-656	-1 888
Dividends paid to shareholders of Novartis AG		-6 645	-6 966	321
Acquisition of treasury shares		-5 530	-1 787	-3 743
Proceeds from exercise options and other treasury share transactions		205	434	-229
Increase in non-current financial debts		93	2 856	-2 763
Repayments of non-current financial debts		-3 194	-366	-2 828
Change in current financial debts		-519	1 199	-1 718
Payments of lease liabilities, net		-183		-183
Receipts from finance sublease receivables		7		7
Impact of change in ownership of consolidated entities		-6	-14	8
Dividends paid to non-controlling interests and other financing cash flows		69	417	-348
Net cash flows used in financing activities from continuing operations		-15 703	-4 227	-11 476
Net cash flows from/used in financing activities from discontinued operations ³		3 279	-470	3 749
Total net cash flows used in financing activities		-12 424	-4 697	-7 727
Net change in cash and cash equivalents before effect of exchange rate changes		-4 883	5 153	-10 036
Effect of exchange rate changes on cash and cash equivalents		-10	-13	3
Total net change in cash and cash equivalents		-4 893	5 140	-10 033
Cash and cash equivalents at January 1		13 271	8 860	4 411
Cash and cash equivalents at September 30		8 378	14 000	-5 622

¹ In 2019, the total net tax payment amounted to USD 1 233 million, of which USD 38 million is included in the line "Net cash flows from operating activities from discontinued operations." In 2018, the total net tax payment amounted to USD 1 319 million, of which USD 75 million was included in the line "Acquisitions and divestments of interests in associated companies, net" and USD 135 million was included in the line "Net cash flows from operating activities from discontinued operations."

² For additional information related to 9M 2019 "Net cash flows used in investing activities from discontinued operations", refer to Note 11.

³ Including USD 190 million (2018: USD 41 million) transaction cost payments directly attributable to the distribution (spin-off) of the Alcon business to Novartis shareholders (see Note 2)

**Notes to the Condensed Interim Consolidated Financial Statements
for the three-month and nine-month period ended September 30, 2019
(unaudited)**

1. Basis of preparation

These Condensed Interim Consolidated Financial Statements for the three-month and nine-month period ended September 30, 2019, were prepared in accordance with International Accounting Standard 34 *Interim Financial Reporting* and accounting policies set out in the 2018 Annual Report published on January 30, 2019.

2. Selected critical accounting policies

The Group's principal accounting policies are set out in Note 1 to the Consolidated Financial Statements in the 2018 Annual Report and conform with International Financial Reporting Standards (IFRS) as issued by the International Accounting Standards Board.

The presentation of financial statements requires management to make subjective and complex judgments that affect the reported amounts. Because of the inherent uncertainties, actual outcomes and results may differ from management's assumptions and estimates.

As disclosed in the 2018 Annual Report, goodwill, and acquired In-Process Research & Development projects are reviewed for impairment at least annually and these, as well as all other investments in intangible assets, are reviewed for impairment whenever an event or decision occurs that raises concern about their balance sheet carrying value. The amount of goodwill and other intangible assets on the Group's consolidated balance sheet has risen significantly in recent years, primarily from acquisitions. Impairment testing may lead to potentially significant impairment charges in the future that could have a materially adverse impact on the Group's results of operations and financial condition.

During the first quarter of 2019, at the Annual General Meeting (AGM) of Novartis AG shareholders, held on February 28, 2019, the Novartis AG shareholders approved a special distribution by way of a dividend in kind to effect the spin-off of Alcon Inc. The shareholder approval required the recognition of a distribution liability at the fair value of the Alcon business to be distributed to Novartis AG shareholders. This required the use of valuation techniques for purposes of impairment testing of the Alcon business' assets to be distributed and for the measurement of the fair value of the distribution liability. These valuations required the use of management assumptions and estimates related to the Alcon business' future cash flows, market multiples to estimate day one market value and control premiums to apply in estimating the Alcon business fair value. These fair value measurements are classified as "Level 3" in the fair value hierarchy. Note 1 and Note 10 to the Consolidated Financial Statements in the 2018 Annual Report provide additional information on key assumptions that are highly sensitive in the estimation of fair values using valuation techniques. Due to these factors and inherent uncertainties in the use of estimates, actual outcomes and results could vary significantly.

The February 28, 2019, shareholder approval for the spin-off required the Alcon Division and selected portions of Corporate activities attributable to Alcon's business (the "Alcon business") to be reported as discontinued operations. Refer to Note 3 and Note 11 for further details.

Transaction costs recorded in Equity

Transaction costs that are directly attributable to the distribution (spin-off) of the Alcon business to the Novartis AG shareholders, and that would otherwise have been avoided, are recorded as a deduction from equity.

Non-current assets held for sale or held for distribution to owners

Non-current assets are classified as assets held for sale or related to discontinued operations when their carrying amount is to be recovered principally through a sale transaction or distribution to owners and a sale or distribution to owners is considered highly probable. They are stated at the lower of carrying amount and fair value less costs to sell with any resulting impairment recognized. Assets

related to discontinued operations and assets of disposal group held for sale are not depreciated or amortized. The December 31, 2018, consolidated balance sheet is not restated.

Distribution liability

The distribution liability was recorded at the date of shareholder approval for the distribution of the business assets to the shareholders. The Group has elected to measure the distribution liability at the fair value of the business assets taken as a whole to be distributed to shareholders. As a result, the distribution liability was recognized based on the fair value of the Alcon business. The distribution liability was recognized through a reduction in retained earnings. It is adjusted at each balance sheet date for changes in its estimated fair value, up to the date of the distribution to shareholders through retained earnings. Any resulting impairment of the business assets to be distributed is recognized in the consolidated income statements in "Other expense" of discontinued operations, at the date of initial recognition of the distribution liability or at subsequent dates resulting from changes of the distribution liability valuation. At the distribution settlement date, any resulting gain, which is measured as the excess amount of the distribution liability over the then carrying value of the assets of the business distributed, is recognized on the line "Gain on distribution of Alcon Inc. to Novartis AG shareholders" in the income statement of discontinued operations.

New IFRS standards effective as of January 1, 2019

IFRS 16 LEASES

IFRS 16 Leases substantially changed the financial statements as the majority of leases for which the company is the lessee became on-balance sheet liabilities with corresponding right-of-use assets also recognized on the balance sheet. The lease liability reflects the net present value of the remaining lease payments, and the right-of-use asset corresponds to the lease liability, adjusted for payments made before the commencement date, lease incentives and other items related to the lease agreement. The standard replaces IAS 17 Leases and related interpretations.

Upon adoption of the new standard, a portion of the annual operating lease costs, which was previously fully recognized as a functional expense, is recorded as interest expense. In addition, the portion of the lease payments which represents the reduction of the lease liability is recognized in the cash flow statement as an outflow from financing activities, which was previously fully recognized as an outflow from operating activities. Given the leases involved and the current low interest rate environment, these effects are not significant to the presentation of our consolidated income statement as well as consolidated cash flows from operating activities and from financing activities.

The Group implemented the new standard on January 1, 2019, and applied the modified retrospective method, with right-of-use assets measured at an amount equal to the lease liability, adjusted by the amount of the prepaid or accrued lease payments relating to those leases recognized in the balance sheet immediately before the date of initial application and will not restate prior years.

Results of our impact assessment:

The undiscounted operating lease commitments as of December 31, 2018, disclosed in Note 27 to the Consolidated Financial Statements in the Annual Report 2018, amounted to USD 3.6 billion. This includes approximately USD 0.1 billion of leases with a commencement date in 2019 and short-term leases, as well as low-value leases that are recognized from January 1, 2019, upon adoption of IFRS 16, on a straight-line basis as expense in profit and loss. This also includes USD 0.2 billion lease commitments related to the Alcon Division, which is attributable to discontinued operation in 2019. For the remaining lease commitments attributable to continuing operations of USD 3.3 billion, the Group recognized on January 1, 2019, lease liabilities of USD 1.74 billion and right-of-use assets USD 1.55 billion (after adjustments for the USD 0.18 billion prepayments and accrued lease payments recognized as at December 31, 2018). For the lease commitments attributable to discontinued operations, the Group recognized on January 1, 2019, lease liabilities and right-of-use assets of USD 0.2 billion. This does not include the discontinued operations right-of-use assets and lease liability on finance lease agreements of USD 75 million and USD 89 million, respectively. There was an insignificant impact to retained earnings upon adoption of IFRS 16 of USD 3 million that arose from subleases that were

accounted for as operating lease agreements under IAS 17 and are accounted for as finance leases under IFRS 16.

As a lessor, the Group had no significant impact upon adoption.

For further information on the impact of adoption and additional disclosures of IFRS 16 Leases, see Note 6.

The Group has updated accounting policies, effective January 1, 2019, upon adoption of IFRS 16 – Leases are as follows:

Leases

As lessee, the Group assesses whether a contract contains a lease at inception of a contract and upon a modification of a contract. The Group elected to allocate the consideration in the contract to the lease component and non-lease component on the basis of its relative stand-alone price.

The Group recognizes a right-of-use asset and a corresponding lease liability for all arrangements in which it is a lessee, except for leases with a term of twelve months or less (short-term leases) and low value leases. For these short-term and low value leases, the Group recognizes the lease payments as an operating expense on a straight-line basis over the term of the lease.

The lease liability is initially measured at the present value of the future lease component payments, as from the commencement date of the lease. The lease payments are discounted using the interest rate implicit in the lease or, if not readily determinable, the Novartis incremental borrowing rate in the respective markets.

The Group remeasures the lease liability (and makes a corresponding adjustment to the related right-of-use asset) whenever there is, a change to the lease terms or expected payments under the lease, or a modification that is not accounted for as a separate lease.

The right-of-use assets are initially recognized on the balance sheet at cost, which comprises the amount of the initial measurement of the corresponding lease liability, adjusted for any lease payments made at or prior to the commencement date of the lease, any lease incentive received and any initial direct costs incurred by Novartis, and expected costs for obligations to dismantle and remove right-of-use assets when they are no longer used.

Right-of-use assets are depreciated on a straight-line basis from the commencement date of the lease over the shorter of the useful life of the right-of-use asset or the end of the lease term.

Right-of-use assets are assessed for impairment whenever there is an indication that the balance sheet carrying amount may not be recoverable using cash flow projections for the useful life.

3. Significant transactions

Significant transaction in 2019

Completion of the spin-off of the Alcon business through a dividend in kind distribution to Novartis AG shareholders

On June 29, 2018, Novartis announced its intention to seek shareholder approval for the spin-off of the Alcon business into a separately traded standalone company, following the complete structural separation of the Alcon business into a standalone company (the Alcon business or Alcon Inc.).

The Novartis AG shareholders approved the spin-off of the Alcon business at the 2019 Annual General Meeting held on February 28, 2019, subject to completion of certain conditions precedent to the distribution. Upon shareholder approval, the Alcon business was reported as discontinued operations and the fair value of the Alcon business exceeded the carrying value of its net assets.

The conditions precedent to the spin-off were met and on April 8, 2019, the spin-off of the Alcon business was effected by way of a distribution of a dividend in kind of Alcon Inc. shares to Novartis AG

shareholders and ADR (American Depositary Receipt) holders (the Distribution). Through the Distribution, each Novartis AG shareholder received 1 Alcon Inc. share for every 5 Novartis AG shares/ADRs they held on April 8, 2019, close of business. As of April 9, 2019, the shares of Alcon Inc. are listed on the SIX Swiss Exchange (SIX) and on the New York Stock Exchange (NYSE) under the symbol "ALC".

The dividend in kind distribution liability to effect the spin-off of the Alcon business (the distribution liability) amounted to USD 26.4 billion at March 31, 2019, unchanged from its initial recognition on February 28, 2019, and was in excess of the carrying value of the Alcon business net assets as of February 28, 2019, and as of March 31, 2019. The net assets of the Alcon business amounted to USD 23.1 billion as at March 31, 2019.

On March 6, 2019, Alcon entered into financing arrangements with a syndicate of banks under which it borrowed on April 2, 2019 a total amount of USD 3.2 billion. These borrowings consisted of approximately USD 2.8 billion and the equivalent of USD 0.4 billion in EUR in bridge and other term loans under such Alcon facilities agreement. In addition, approximately USD 0.3 billion of borrowings under a number of local bilateral facilities in different countries, with the largest share of borrowings in Japan, were raised. This resulted in a total gross debt of USD 3.5 billion. These outstanding borrowings of the Alcon legal entities were recorded in the balance sheet and financing cash flow from discontinued operations. Prior to the spin-off, through a series of intercompany transactions, Alcon legal entities paid approximately USD 3.1 billion in cash to Novartis and its affiliates.

At the April 8, 2019 Distribution, the fair value of the distribution liability of the Alcon business amounted to USD 23.4 billion, a decrease of USD 3.0 billion from March 31, 2019. As mentioned above, prior to the spin-off, through a series of intercompany transactions, Alcon legal entities incurred additional net financial debt and paid approximately USD 3.1 billion in cash to Novartis and its affiliates. This additional net debt and transactions resulted in a decrease in Alcon's net assets to USD 20.0 billion at the date of the Distribution of the dividend in kind to Novartis AG shareholders on April 8, 2019. The distribution liability at April 8, 2019, remained in excess of the then carrying value of the Alcon business net assets.

Certain consolidated foundations own Novartis AG dividend bearing shares restricting their availability for use by the Group. These Novartis AG shares are accounted for as treasury shares. Through the Distribution, these foundations received Alcon Inc. shares representing an approximate 4.7% equity interest in Alcon Inc. Upon the loss of control of Alcon Inc. through the Distribution, the financial investment in Alcon Inc. was recognized at its fair value based on the opening traded share price of Alcon Inc. on April 9, 2019 (a Level 1 hierarchy valuation). At initial recognition, its fair value of USD 1.3 billion was reported on the Group's consolidated balance sheet as a financial asset. Management has designated this investment at fair value through other comprehensive income.

The total non-taxable non-cash gain recognized at the completion of the spin-off of the Alcon business on April 9, 2019, amounted to USD 4.7 billion consisting of:

(USD millions)

Net assets derecognized ¹	-20 025
Derecognition of distribution liability	23 434
Difference between net assets and distribution liability	3 409
Recognition of Alcon Inc. shares obtained through consolidated foundations	1 273
Currency translation gains recycled into the consolidated income statement	123
Transaction costs recognized in the consolidated income statement	-114
Gain on distribution of Alcon Inc. to Novartis AG shareholders	4 691

¹ See Note 11 for additional information.

Significant transaction closed in 2019 – Continuing operations

Innovative Medicines – Acquisition of IFM Tre, Inc.

On May 7, 2019, Novartis acquired IFM Tre, Inc., a privately held, US based biopharmaceutical company focused on developing anti-inflammatory medicines targeting the NLRP3 inflammasome. The acquisition gives Novartis full rights to IFM Tre, Inc.'s portfolio of NLRP3 antagonists. The NLRP3 antagonists portfolio consists of one clinical and two pre-clinical programs: IFM-2427, a first-in-class, clinical stage systemic antagonist for an array of chronic inflammatory disorders including atherosclerosis and nonalcoholic steatohepatitis (NASH); a pre-clinical stage gutdirected molecule for the treatment of inflammatory bowel disease; and a pre-clinical stage central nervous system (CNS)-penetrant molecule.

The previously held interest of 9% is adjusted to its preliminary fair value of USD 33 million through the consolidated income statement at acquisition date. This remeasurement resulted in a gain of USD 14 million. The preliminary fair value of the total purchase consideration for acquiring the 91% stake Novartis did not already own amounted to USD 361 million. The amount consisted of an initial cash payment of USD 285 million and the preliminary net present value of the contingent consideration of USD 76 million due to the IFM Tre, Inc. shareholders, which they are eligible to receive upon the achievement of specified development and commercialization milestones. The preliminary purchase price allocation resulted in net identifiable assets of USD 355 million, mainly intangibles, and goodwill of USD 39 million. Results of operations since the date of acquisition were not material.

Innovative Medicines – Acquisition of Xiidra

On May 8, 2019, Novartis entered into an agreement with Takeda Pharmaceutical Company Limited (Takeda) to acquire the assets associated with *Xiidra* (lifitegrast ophthalmic solution) 5% worldwide. *Xiidra* is the first and only prescription treatment approved to treat both signs and symptoms of dry eye by inhibiting inflammation caused by the disease. The transaction bolsters the Novartis front-of-the-eye portfolio and ophthalmic leadership. The transaction closed on July 1, 2019. The purchase price consists of an USD 3.4 billion upfront payment, customary purchase price adjustments of USD 0.1 billion and the potential milestone payments up to USD 1.9 billion, which Takeda is eligible to receive upon the achievement of specified commercialization milestones.

The fair value of the total purchase consideration is USD 3.7 billion. The amount consists of an initial cash payment of USD 3.5 billion and the net present value of the contingent consideration of USD 0.2 billion, which Takeda is eligible to receive upon the achievement of specified commercialization milestones.

The preliminary purchase price allocation resulted in net identifiable assets of approximately USD 3.6 billion, consisting mainly of intangible assets of USD 3.6 billion and goodwill amounted to approximately USD 0.1 billion. In 2019, from the date of acquisition, the business generated net sales of USD 0.1 billion. Management estimates net sales for the nine-month period ended September 30, 2019, would have amounted to USD 0.2 billion, had the business been acquired at the beginning of the 2019 reporting period. Results of operations since the date of acquisition were not material.

For significant transactions closed in 2019 for Discontinued operations, see Note 11.

Significant pending transaction

Sandoz – Divestment of US dermatology business and generic US oral solids portfolio

On September 6, 2018, Novartis announced it has agreed to sell selected portions of its Sandoz US portfolio, specifically the Sandoz US dermatology business and generic US oral solids portfolio, to Aurobindo Pharma USA Inc. (Aurobindo), for USD 0.8 billion in cash and potential earn-outs.

The Sandoz US portfolios to be sold to Aurobindo include approximately 300 products as well as additional development projects. The sale includes the Sandoz US generic and branded dermatology businesses as well as its dermatology development center. As part of the transaction, Aurobindo will acquire the manufacturing facilities in Wilson, North Carolina, and in Hicksville and Melville, New York.

The transaction is expected to be completed in the coming months, pending regulatory approval. As the fair value of the consideration (USD 0.8 billion) less costs to sell was below the carrying value of

the divested business (USD 1.0 billion, which includes an allocation of Sandoz goodwill of USD 0.2 billion), an impairment of the net assets to be divested in the amount of USD 0.2 billion was recognized as a reduction to goodwill.

In the Group's consolidated balance sheet at September 30, 2019 and at December 31, 2018, the business assets and liabilities of the Sandoz US dermatology business and generic US oral solids portfolio are separately shown as assets and liabilities of disposal group held for sale.

The disposal group, assets and liabilities classified as held for sale consist of the following:

(USD millions)	Sep 30, 2019	Dec 31, 2018
Assets of disposal group classified as held for sale		
Property, plant and equipment	163	148
Intangible assets other than goodwill	474	478
Deferred tax assets	10	8
Other non-current assets	2	1
Inventories	186	165
Other current assets	10	7
Total	845	807
Liabilities of disposal group classified as held for sale		
Deferred tax liabilities	2	2
Provisions and other non-current liabilities	4	4
Provisions and other current liabilities	18	45
Total	24	51

There are no cumulative income or expenses included in other comprehensive income relating to the disposal group.

Significant transactions in 2018

Innovative Medicines – Acquisition of Advanced Accelerator Applications S.A.

On October 30, 2017, Novartis entered into a binding memorandum of understanding with Advanced Accelerator Applications S.A. (AAA), a company headquartered in Saint-Genis-Pouilly, France, under which Novartis agreed to commence a tender offer for 100% of the share capital of AAA subject to certain conditions. Novartis commenced the tender offer on December 7, 2017, to purchase all of the outstanding ordinary shares for a price of USD 41 per share and USD 82 per American Depositary Share (ADS), each representing two ordinary shares of AAA, which expired on January 19, 2018. The offer valued AAA's equity at USD 3.9 billion, on a fully diluted basis.

As of January 19, 2018, the expiration date of the tender offer, approximately 97% of the then-outstanding fully diluted ordinary shares, including ordinary shares represented by ADSs (hereinafter collectively referred to as "the outstanding shares"), were validly tendered. On January 22, 2018, Novartis accepted and paid USD 3.9 billion for the outstanding shares tendered in the offer. On January 22, 2018, Novartis commenced a subsequent offering period that expired on January 31, 2018. As of the expiration of the subsequent offering period, an additional 1.8% of the outstanding shares were validly tendered. Novartis accepted and paid approximately USD 60 million, resulting in an increase in Novartis ownership in AAA to 98.7%.

The fair value of the total purchase consideration was USD 3.9 billion. The purchase price allocation resulted in net identifiable assets of approximately USD 1.9 billion, consisting of USD 2.5 billion intangible assets, USD 0.6 billion net deferred tax liabilities, and goodwill of approximately USD 2.0 billion. In 2018, from the date of the acquisition the business generated net sales of USD 0.4 billion. Management estimates net sales for the entire year 2018 would have amounted to USD 0.4 billion had AAA been acquired at the beginning of 2018. The 2018 results from operations since the date of the acquisition were not material.

As of December 31, 2018, Novartis held 99.1% of the then-outstanding fully diluted ordinary shares, including ordinary shares represented by ADSs.

AAA is a radiopharmaceutical company that develops, produces and commercializes molecular nuclear medicines – including Lutathera (USAN: lutetium Lu 177 dotatate/INN: lutetium (177Lu) oxodotreotide), a first-in-class radioligand therapy product for neuroendocrine tumors – and a portfolio of diagnostic products. Radiopharmaceuticals, such as Lutathera, are unique medicinal formulations containing radioisotopes, which are used clinically for both diagnosis and therapy.

Innovative Medicines – Acquisition of AveXis, Inc.

On April 6, 2018, Novartis entered into an agreement and plan of merger with AveXis, Inc., a US-based clinical stage gene therapy company, under which Novartis commenced on April 17, 2018, a tender offer to purchase all outstanding common stock of AveXis, Inc. for USD 218 per share in cash. On May 15, 2018, Novartis completed the acquisition of the common stock of AveXis, Inc. and paid a total of USD 8.7 billion.

The fair value of the total purchase consideration was USD 8.7 billion. The purchase price allocation resulted in net identifiable assets of approximately USD 7.2 billion, consisting of USD 8.5 billion intangible assets, USD 1.6 billion net deferred tax liabilities and other net assets of USD 0.3 billion, and goodwill of approximately USD 1.5 billion. The 2018 results of operations since the date of acquisition were not material.

AveXis, Inc. is focused on developing and commercializing novel treatments for patients suffering from rare and life-threatening neurological genetic diseases. AveXis, Inc.'s initial product candidate, AVXS-101, is a proprietary gene therapy currently in development for the treatment of spinal muscular atrophy (SMA) type 1 – the leading genetic cause of infant mortality – and SMA types 2 and 3. In addition, AveXis, Inc. has a pipeline of other novel treatments for rare neurological diseases, including Rett syndrome (RTT) and a genetic form of amyotrophic lateral sclerosis (ALS) caused by mutations in the superoxide dismutase 1 (SOD1) gene.

Innovative Medicines – Acquisition of Endocyte, Inc.

On October 18, 2018, Novartis entered into an agreement and plan of merger with Endocyte, a US-based bio-pharmaceutical company focused on developing targeted therapeutics for cancer treatment. The transaction was completed on December 21, 2018. Under the terms of the agreement, Novartis acquired all outstanding shares of Endocyte common stock for USD 24 per share. The total consideration amounted to USD 2.1 billion.

The fair value of the total purchase consideration was USD 2.1 billion. The preliminary purchase price allocation resulted in net identifiable assets of approximately USD 1.5 billion, consisting of USD 1.4 billion intangible assets, USD 0.2 billion net deferred tax liabilities and other net assets of USD 0.3 billion, and goodwill of approximately USD 0.6 billion. The purchase price allocation remains preliminary and will be finalized within the 12-month purchase price allocation measurement period, which started as of the acquisition date. Adjustments made to the December 31, 2018, preliminary purchase price allocation were not material and the Group currently does not expect any potential additional revisions to be material. The 2018 results from operations since the date of the acquisition were not material.

Endocyte uses drug conjugation technology to develop targeted therapies with companion imaging agents, including 177Lu-PSMA-617, a potential first-in-class investigational radioligand therapy for the treatment of metastatic castration-resistant prostate cancer (mCRPC).

Corporate – Divestment of 36.5% stake in GlaxoSmithKline Consumer Healthcare Holdings Ltd.

On March 27, 2018, Novartis entered into an agreement with GlaxoSmithKline plc (GSK) to divest its 36.5% stake in GlaxoSmithKline Consumer Healthcare Holdings Ltd. to GSK for USD 13.0 billion in cash. As a result, Novartis discontinued the use of equity method accounting starting from April 1, 2018.

On June 1, 2018, the transaction closed and Novartis realized a pre-tax gain of USD 5.8 billion, recorded in income from associated companies.

4. Summary of equity attributable to Novartis AG shareholders

	Number of outstanding shares (in millions)			Issued share capital and reserves attributable to Novartis AG shareholders (in USD millions)		
	2019	2018	Change	9M 2019	9M 2018	Change
Balance at beginning of year	2 311.2	2 317.5	-6.3	78 614	74 168	4 446
Impact of change in accounting policy ¹				3	60	-57
Restated equity at January 1				78 617	74 228	4 389
Shares acquired to be cancelled	-60.3	-21.2	-39.1	-5 351	-1 684	-3 667
Other share purchases	-1.7	-1.4	-0.3	-156	-107	-49
Exercise of options and employee transactions	5.5	7.8	-2.3	200	434	-234
Equity-based compensation	9.9	7.3	2.6	641	555	86
Shares delivered to Alcon employees as a result of the Alcon spin-off				32		32
Taxes on treasury share transactions ²				-189		-189
Decrease/(increase) of treasury share repurchase obligation under a share buyback trading plan				284	-889	1 173
Dividends to shareholders of Novartis AG				-6 645	-6 966	321
Dividend in kind ³				-23 434		-23 434
Net income of the period attributable to shareholders of Novartis AG				10 607	11 416	-809
Other comprehensive income attributable to shareholders of Novartis AG				-1 841	960	-2 801
Transaction costs ⁴				-253	-39	-214
Impact of change in ownership of consolidated entities				-3	1	-4
Other movements ⁵				15	29	-14
Balance at September 30	2 264.6	2 310.0	-45.4	52 524	77 938	-25 414

¹ In 2019, the impact of change in accounting policy includes USD 3 million related to the implementation of IFRS 16 – Leases (see Notes 2 and 6 for further details).

In 2018, the impact of change in accounting policy includes USD 60 million relating to the implementation of IFRS 15 – Revenue from Contracts with Customers implementation and USD 177 million relating to the implementation IFRS 9 – Financial instruments (see Note 1 and 29 of the 2018 Annual report)

² Included in 2019 is a USD 69 million impact related to the revaluation of deferred tax liability on treasury shares that are recognized through retained earnings. This revaluation resulted from the Swiss Federal tax reform enacted in May 2019, effective January 1, 2020.

³ Fair value of the dividend-in-kind of Alcon Inc. shares to Novartis AG shareholders and ADR (American Depositary Receipt) holders approved at the 2019 Annual General Meeting held on February 28, 2019. Distribution was effected on April 8, 2019, whereby each Novartis AG shareholders and ADR holder received 1 Alcon Inc. share for every 5 Novartis AG shares/ADRs they held on April 8, 2019, close of business (see Note 2, 3 and 11 for further details)

⁴ Transaction costs directly attributable to the distribution (spin-off) of the Alcon business to Novartis AG shareholders (see Note 2)

⁵ Impact of hyperinflationary economies

5. Financial instruments

Fair value by hierarchy

The following table illustrates the three hierarchical levels for valuing financial instruments at fair value and those measured at amortized cost as of September 30, 2019 and December 31, 2018. For additional information on the hierarchies and other matters, please refer to the Consolidated Financial Statements in the 2018 Annual Report, published on January 30, 2019.

	Level 1		Level 2		Level 3		Valued at amortized cost or cost		Total	
	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018
(USD millions)										
Debt securities		302	24	23					24	325
Fund investments	37	35							37	35
Total marketable securities	37	337	24	23					61	360
Time deposits and short term investments with original maturity more than 90 days							81	2 087	81	2 087
Derivative financial instruments			86	130					86	130
Accrued interest on debt securities								12		12
Total marketable securities, time deposits and derivative financial instruments	37	337	110	153			81	2 099	228	2 589
Financial investments and long-term loans										
Financial investments	1 238	698			639	488			1 877	1 186
Fund investments					223	251			223	251
Contingent consideration receivables					409	396			409	396
Long-term loans and receivables from customers and finance lease, advances, security deposits							269	512	269	512
Financial investments and long-term loans	1 238	698			1 271	1 135	269	512	2 778	2 345
Associated companies at fair value through profit or loss					174	145			174	145
Contingent consideration payables					-1 065	-907			-1 065	-907
Other financial liabilities					-36	-10			-36	-10
Derivative financial instruments			-154	-58					-154	-58
Total financial liabilities at fair value			-154	-58	-1 101	-917			-1 255	-975

There were no significant transfers from one level to the other and no significant transactions associated with level 3 financial instruments.

The fair value of straight bonds amounted to USD 23.7 billion at September 30, 2019 (USD 25.4 billion at December 31, 2018) compared to the balance sheet value of USD 21.9 billion at September 30, 2019 (USD 25.3 billion at December 31, 2018). For all other financial assets and liabilities, the carrying amount is a reasonable approximation of the fair value. The carrying amount of financial assets included in the line financial investments and long-term loans of USD 2.8 billion at September 30, 2019 (USD 2.3 billion at December 31, 2018) is included in line "Financial and other non-current assets" of the consolidated balance sheets.

During the third quarter of 2019, Alcon Inc. shares with a fair value of USD 543 million (USD 656 million in the nine-month period ended September 30, 2019) were sold and the USD 39 million (USD 48 million in the nine-month period ended September 30, 2019) gain on disposal was transferred from other comprehensive income to retained earnings.

The Group's exposure to financial risks has not changed significantly during the period and there have been no major changes to the risk management department or in any risk management policies.

6. Right-of-use assets and lease liabilities

Note 2 explains the changes and new accounting policy introduced on January 1, 2019, resulting from the adoption of the new accounting standards IFRS 16 – Leases.

On transition to IFRS 16, the Group elected to apply the practical expedient to not reassess whether a contract is, or contains, a lease at January 1, 2019, the implementation date of IFRS 16. As a result, at the date of implementation, the Group applied IFRS 16 only to contracts that were previously identified as leases under IAS 17 – Leases and related interpretations, and the definition of a lease under IFRS 16 was applied only to contracts entered into or changed on or after 1 January 2019.

The impact on retained earnings upon implementation of IFRS 16 was USD 3 million arising from subleases that were accounted for as operating lease agreements under IAS 17 and are accounted for as finance leases under IFRS 16.

The Group has entered into various fixed-term leases, mainly for vehicles and real estate.

The lease liabilities recorded in continuing operations on January 1, 2019, were USD 1.7 billion and the right-of-use assets were USD 1.6 billion.

Reconciliation of lease commitment disclosed on December 31, 2018, and lease liabilities recorded in continuing operations on January 1, 2019, are as follows:

(USD millions)

Operating lease commitments December 31, 2018 ¹	3 612
Operating lease commitments December 31, 2018 related to discontinued operations	-222
Operating lease commitments December 31, 2018 related to continuing operations	3 390
Recognition exemption for short term leases	-30
Recognition exception for low value leases	-12
Lease arrangements with commencement date after December 31, 2018	-65
Undiscounted future lease payments continuing operations as of January 1, 2019	3 283
Effect of discounting	-1 547
Lease liabilities as of January 1, 2019²	1 736

¹ As reported in Annual Report 2018 Note 27

² Weighted average incremental borrowing rate of 3.5% was applied at January 1, 2019, the date of implementation of IFRS 16 – Leases.

The right-of-use assets of continuing operations at January 1, 2019, by underlying class of asset comprise the following:

(USD millions)	January 1, 2019
Land	536
Buildings	848
Vehicles	147
Machinery and equipment and other assets	23
Right-of-use assets¹	1 554

¹ Right-of-use assets were lower than the lease liabilities at the date of implementation of IFRS 16 by USD 182 million, due to adjustments made for prepayments and accrued lease payments recognized at December 31, 2018.

The lease liabilities recorded in discontinued operations on January 1, 2019, were USD 286 million and the right-of-use assets were USD 276 million, including USD 89 million and USD 75 million, respectively, for the previously reported finance lease obligations.

As a result of applying the modified retrospective method at the date of implementation of IFRS 16 on January 1, 2019, whereby the right-of-use assets were measured at the amount equal to the lease liabilities, there is no impact to the reported deferred tax assets and deferred tax liabilities on the consolidated balance sheet, as the corresponding deferred tax assets and deferred tax liabilities attributable to the lease liabilities and right-of-use assets relate to income taxes levied by the same taxation authority within the same legal entity, and were therefore offset.

The following table summarizes the movements of the right-of-use assets of continuing operations:

(USD millions)

Right-of-use assets at January 1, 2019	1 554
Additions ¹	428
Depreciation charge	-227
Lease contract terminations ²	-63
Currency translation effects	-10
Total right-of-use assets at September 30, 2019	1 682

No impairments were recorded in the period.

¹ Additions in Q3 amounted to USD 29 million.

² Lease contract terminations represent modifications to existing leases that result in reductions to the right-of-use assets, which includes contract terminations.

The right-of-use assets carrying value and depreciation charge of continuing operations at September 30, 2019, are shown below by underlying class of asset:

(USD millions)	September 30, 2019 Carrying value	Depreciation charge	
		Q3 2019	9M 2019
Land	538	2	10
Buildings	989	50	147
Vehicles	133	24	65
Machinery and equipment and other assets	22	2	5
Total right-of-use assets	1 682	78	227

The lease liabilities of continuing operations at September 30, 2019, amounted to USD 2.0 billion and its breakdown by maturity is as follows:

(USD millions)	September 30, 2019
Less than one year	266
Between one and two years	201
Between two and three years	163
Between three and four years	138
Between four and five years	121
After five years	1 079
Total lease liabilities	1 968

The following table provides additional disclosures related to right-of-use assets and lease liabilities of continuing operations:

(USD millions)	Q3 2019	9M 2019
Interest expense on lease liabilities ¹	18	50
Expense on short-term leases ²	2	6
Expense on low-value leases ²	3	7
Total cash outflow for leases	108	219
<i>Thereof repayment of lease liabilities³</i>	<i>92</i>	<i>183</i>
Gain arising from sale and leaseback transaction	0	468

¹ Weighted average interest rate is 3.2% and 3.6% for Q3 2019 and 9M 2019, respectively.

² Cash flows from short-term and low value leases are included within total net cash flows from operating activities

³ Reported as cash outflows used in financing activities net of lease incentives received of USD 33 million in 9M 2019 (Q3 2019: USD 4 million)

There were no variable lease payments not included in the measurement of the lease liabilities.

The net investment held and the income from subleasing right-of-use assets was not significant.

In the second quarter 2019, the Group completed a sale and leaseback transaction for certain property plant and equipment as part of its plans to consolidate sites. The transaction resulted in net cash flow inflows of USD 0.6 billion and the recognition of USD 86 million of lease liabilities, and USD 30 million of right-of-use assets. The right-of-use assets value reflects the proportion of the property, plant and equipment retained for a period of 1 to 5 years, with two 5 year extension periods for certain right-of-use assets, and the liabilities reflect the net present value of future lease payments. The net gain on the sale and leaseback transaction amounted to USD 0.5 billion.

Following the completion of the Alcon Distribution (spin-off) on April 9, 2019, the right-of-use assets and lease liabilities classified as discontinued operations were derecognized (refer to Note 2, 3 and 11 for further details).

7. Details to the consolidated statements of cash flows

Reversal of non-cash items and other adjustments

(USD millions)	Q3 2019	Q3 2018	Change
Depreciation, amortization and impairments on:			
Property, plant and equipment	524	454	70
Intangible assets	878	911	-33
Financial assets ¹	-29	57	-86
Non-cash change in provisions and other non-current liabilities	382	178	204
Gains on disposal and other adjustments on property, plant and equipment; intangible assets; financial assets; and other non-current assets, net	-17	-368	351
Equity-settled compensation expense	216	169	47
Income from associated companies	-253	-213	-40
Taxes	366	369	-3
Net financial expense	204	201	3
Total	2 271	1 758	513

¹ Includes fair value adjustments

(USD millions)	9M 2019	9M 2018	Change
Depreciation, amortization and impairments on:			
Property, plant and equipment	1 392	1 307	85
Intangible assets	2 497	2 268	229
Financial assets ¹	-49	-49	0
Non-cash change in provisions and other non-current liabilities	1 400	425	975
Gains on disposal and other adjustments on property, plant and equipment; intangible assets; financial assets; and other non-current assets, net	-701	-779	78
Equity-settled compensation expense	588	506	82
Income from associated companies ²	-509	-6 297	5 788
Taxes	1 163	1 182	-19
Net financial expense	591	576	15
Total	6 372	-861	7 233

¹ Includes fair value adjustments

² 2018 includes a reversal of a pre-tax gain (USD 5.8 billion) recognized from the divestment of the investment in GSK Consumer Healthcare Holdings Ltd. (see Note 3). The net cash proceed of USD 13.0 billion from the divestment was included in the consolidated statements of cash flows in line "Acquisitions and divestments of interests in associated companies, net."

Cash flows arising from acquisitions and divestments of businesses, net

(USD millions)	Q3 2019	Q3 2018	9M 2019	9M 2018
Net assets recognized as a result of business combinations	-3 651		-4 124	-11 848
Fair value of previously held equity interests			33	
Receivables and payables contingent consideration, net	166		242	-5
Other payments and deferred consideration, net			-3	-37
Cash flows used for acquisitions of businesses	-3 485		-3 852	-11 890
Cash flows from/used in divestments of businesses ¹	25	-20	10	11
Cash flows used for acquisitions and divestments of businesses, net	-3 460	-20	-3 842	-11 879

¹ In 2019 the USD 10 million (Q3 2019: USD 25 million) includes USD 19 million (Q3 2019: USD 4 million) net cash outflows from previous years divestments and USD 29 million net cash inflows in the current year quarter from business divestments in 2019. The net identifiable assets of the 2019 divested businesses amounts to USD 63 million, comprised of non-current asset of USD 65 million, current assets of USD 9 million, non-current liabilities USD 7 million and current liabilities of USD 4 million. In 2018, the USD 11 million represents the net cash inflows from previous years divestments (Q3 2018: USD 20 million net cash outflows).

For net cash flows used in investing activities from discontinued operations, see Note 11.

8. Acquisitions of businesses

(USD millions)	9M 2019	9M 2018
Property, plant and equipment	44	135
Currently marketed products	3 550	2 230
Acquired research and development	433	8 584
Other intangible assets	0	1
Deferred tax assets	52	242
Financial and other assets	8	17
Inventories	186	17
Trade receivables and other current assets	4	81
Cash and cash equivalents		809
Deferred tax liabilities	-123	-2 656
Current and non-current financial debts	-2	-14
Trade payables and other liabilities	-167	-431
Net identifiable assets acquired	3 985	9 015
Acquired cash and cash equivalents		-809
Non-controlling interests		-27
Goodwill	139	3 669
Net assets recognized as a result of business combinations	4 124	11 848

9. Legal proceedings update

A number of Novartis companies are, and will likely continue to be, subject to various legal proceedings, including litigations, arbitrations and governmental investigations, that arise from time to time. Legal proceedings are inherently unpredictable. As a result, the Group may become subject to substantial liabilities that may not be covered by insurance and may in the future incur judgments or enter into settlements of claims that could have a material adverse effect on its results of operations or cash flow. Note 19 to the Consolidated Financial Statements in our 2018 Annual Report and 2018 Form 20-F contains a summary as of the date of these reports of significant legal proceedings to which Novartis or its subsidiaries were a party. The following is a summary as of October 21, 2019 of significant developments in those proceedings, as well as any new significant proceedings commenced since the date of the 2018 Annual Report and 2018 Form 20-F.

INVESTIGATIONS AND RELATED LITIGATIONS

Southern District of New York (S.D.N.Y.) marketing practices investigation and litigation

In 2013, the US government filed a civil complaint in intervention to an individual *qui tam* action against Novartis Pharmaceuticals Corporation (NPC) in the United States District Court for the S.D.N.Y. The complaint, as subsequently amended, asserts federal False Claims Act and common law claims with respect to speaker programs and other promotional activities for certain NPC cardiovascular medications (including *Lotrel*, *Starlix* and *Valturna*) allegedly serving as mechanisms to provide kickbacks to healthcare professionals from 2002 to 2011. It seeks damages and disgorgement of Novartis profits from the alleged unlawful conduct which, based on the government's calculation, with trebling and penalties could exceed USD 1 billion. Also in 2013, New York State filed a civil complaint in intervention asserting similar claims. Neither government complaint in intervention adopted the individual relator's claims with respect to off-label promotion of *Valturna*, which were subsequently dismissed with prejudice by the court. The individual relator continues to litigate the kickback claims on behalf of other states and municipalities. Novartis is engaged in settlement discussions to resolve the above-described claims and has recorded a provision in the amount of USD 0.7 billion in Q2 2019.

In addition to the matter described above, there have been other developments in the other legal matters described in Note 19 to the Consolidated Financial Statements contained in our 2018 Annual Report and 2018 Form 20-F.

The developments during the third quarter of 2019 do not significantly affect the assessment of management concerning the adequacy of the total provisions recorded for legal proceedings.

10. Segmentation of key figures

The businesses of Novartis are divided operationally on a worldwide basis into two identified reporting segments, Innovative Medicines and Sandoz. In addition, we separately report Corporate activities.

Reporting segments are presented in a manner consistent with the internal reporting to the chief operating decision maker which is the Executive Committee of Novartis. The reporting segments are managed separately because they each research, develop, manufacture, distribute and sell distinct products that require differing marketing strategies.

The Executive Committee of Novartis is responsible for allocating resources and assessing the performance of the reporting segments.

The reporting segments are as follows:

Innovative Medicines researches, develops, manufactures, distributes and sells patented prescription medicines. The Innovative Medicines Division is organized into two global business units: Novartis Oncology and Novartis Pharmaceuticals. Novartis Oncology consists of the global business franchise Oncology, and Novartis Pharmaceuticals consists of the global business franchises Ophthalmology; Neuroscience; Immunology, Hepatology and Dermatology; Respiratory; Cardiovascular, Renal and Metabolism; and Established Medicines.

Sandoz develops, manufactures and markets finished dosage form medicines as well as intermediary products including active pharmaceutical ingredients. Sandoz is organized globally into three franchises: Retail Generics, Anti-Infectives and Biopharmaceuticals. In Retail Generics, Sandoz develops, manufactures and markets active ingredients and finished dosage forms of pharmaceuticals to third parties. Retail Generics includes the areas of cardiovascular, central nervous system, dermatology, gastrointestinal and hormonal therapies, metabolism, oncology, ophthalmics, pain and respiratory, as well as finished dosage form anti-infectives sold to third parties. In Anti-Infectives, Sandoz manufactures and supplies active pharmaceutical ingredients and intermediates, mainly antibiotics, for internal use by Retail Generics and for sale to third-party customers. In Biopharmaceuticals, Sandoz develops, manufactures and markets protein- or other biotechnology-based products, including biosimilars, and provides biotechnology manufacturing services to other companies.

The divisions are supported by Novartis Institutes for BioMedical Research, Global Drug Development, Novartis Technical Operations and Novartis Business Services. Corporate includes the costs of the Group headquarters and those of corporate coordination functions in major countries, and items that are not specific to one segment. Further details are provided in Note 3 to the Consolidated Financial Statements of the Annual Report 2018.

Following the February 28, 2019, shareholders' approval of the spin-off of the Alcon business, the Group reported its financial results for the current and prior years as "continuing operations" and "discontinued operations" (refer to Notes 2, 3 and 11 for further details).

Continuing operations comprise the activities of Innovative Medicines and Sandoz Divisions and the continuing Corporate activities.

Discontinued operations include the operational results from the Alcon eye care devices business and certain Corporate activities attributable to the Alcon business prior to the spin-off, the gain on distribution of Alcon Inc. to Novartis AG shareholders and certain other expenses related to the Distribution (See Note 2, 3 and 11).

Segmentation – Consolidated income statement – Third quarter

(USD millions)	Innovative Medicines		Sandoz		Corporate (including eliminations)		Group	
	Q3 2019	Q3 2018	Q3 2019	Q3 2018	Q3 2019	Q3 2018	Q3 2019	Q3 2018
Net sales to third parties from continuing operations	9 688	8 596	2 484	2 420			12 172	11 016
Sales to continuing and discontinued segments	190	206	42	49	-232	-227		28
Net sales from continuing operations	9 878	8 802	2 526	2 469	-232	-227	12 172	11 044
Other revenues	295	299	7	38	8	5	310	342
Cost of goods sold	-2 679	-2 341	-1 354	-1 364	257	242	-3 776	-3 463
Gross profit from continuing operations	7 494	6 760	1 179	1 143	33	20	8 706	7 923
Selling, general and administration	-2 868	-2 614	-532	-534	-149	-113	-3 549	-3 261
Research and development	-2 002	-1 951	-197	-196			-2 199	-2 147
Other income	86	354	40	186	70	56	196	596
Other expense	-306	-365	-299	-241	-191	-266	-796	-872
Operating income from continuing operations	2 404	2 184	191	358	-237	-303	2 358	2 239
<i>as % of net sales</i>	<i>24.8%</i>	<i>25.4%</i>	<i>7.7%</i>	<i>14.8%</i>			<i>19.4%</i>	<i>20.3%</i>
Income from associated companies			1	1	252	212	253	213
Interest expense							-216	-229
Other financial income and expense, net							12	28
Income before taxes from continuing operations							2 407	2 251
Taxes							-366	-369
Net income from continuing operations							2 041	1 882
Net loss from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders								-258
Net loss from discontinued operations								-258
Net income							2 041	1 624

Segmentation – Consolidated income statement – Nine months to September 30

(USD millions)	Innovative Medicines		Sandoz		Corporate (including eliminations)		Group	
	9M 2019	9M 2018	9M 2019	9M 2018	9M 2019	9M 2018	9M 2019	9M 2018
Net sales to third parties from continuing operations	27 794	25 870	7 248	7 400			35 042	33 270
Sales to continuing and discontinued segments	616	551	118	140	-681	-630	53	61
Net sales from continuing operations	28 410	26 421	7 366	7 540	-681	-630	35 095	33 331
Other revenues	806	807	41	48	19	16	866	871
Cost of goods sold	-7 230	-6 973	-3 945	-4 166	742	667	-10 433	-10 472
Gross profit from continuing operations	21 986	20 255	3 462	3 422	80	53	25 528	23 730
Selling, general and administration	-8 432	-7 947	-1 644	-1 729	-388	-364	-10 464	-10 040
Research and development	-5 960	-5 665	-589	-590			-6 549	-6 255
Other income	1 008	862	122	426	258	177	1 388	1 465
Other expense	-1 525	-934	-605	-434	-510	-491	-2 640	-1 859
Operating income from continuing operations	7 077	6 571	746	1 095	-560	-625	7 263	7 041
<i>as % of net sales</i>	<i>25.5%</i>	<i>25.4%</i>	<i>10.3%</i>	<i>14.8%</i>			<i>20.7%</i>	<i>21.2%</i>
Income from associated companies	1		2	5	506	6 292	509	6 297
Interest expense							-647	-684
Other financial income and expense, net							56	108
Income before taxes from continuing operations							7 181	12 762
Taxes							-1 163	-1 182
Net income from continuing operations							6 018	11 580
Net loss from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders							-101	-160
Gain on distribution of Alcon Inc. to Novartis AG shareholders							4 691	
Net income/loss from discontinued operations							4 590	-160
Net income							10 608	11 420

Segmentation – Additional consolidated balance sheet disclosure¹

(USD millions)	Innovative Medicines		Sandoz		Alcon		Corporate (including eliminations)		Group	
	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018	Sep 30, 2019	Dec 31, 2018
Net operating assets	56 617	53 999	13 372	13 951	24 007				72 029	94 876
Included in net operating assets are:										
Property, plant and equipment	9 466	10 098	1 897	2 159	2 878		515	561	11 878	15 696
Goodwill	18 636	18 551	7 663	7 837	8 899		7	7	26 306	35 294
Intangible assets other than goodwill	28 017	26 042	1 626	1 875	10 679		51	123	29 694	38 719

¹ From February 28, 2019, the Alcon Division was reported as discontinued operations (see Note 2, 3 and 11). In accordance with IFRS, the December 31, 2018 consolidated balance sheet includes the assets and liabilities of the Alcon eye care devices business and certain Corporate assets and liabilities attributable to the Alcon business.

Segmentation – Net sales by region¹ – Third quarter

	Q3 2019 USD m	Q3 2018 USD m	% change		Q3 2019 % of total	Q3 2018 % of total
			USD	cc ²		
Innovative Medicines						
Europe	3 195	3 027	6	10	33	35
US	3 725	3 003	24	24	38	35
Asia/Africa/Australasia	2 112	1 929	9	10	22	22
Canada and Latin America	656	637	3	9	7	8
Total	9 688	8 596	13	15	100	100
<i>Of which in Established Markets</i>	7 405	6 518	14	15	76	76
<i>Of which in Emerging Growth Markets</i>	2 283	2 078	10	13	24	24
Sandoz						
Europe	1 297	1 204	8	12	52	50
US	655	661	-1	-1	26	27
Asia/Africa/Australasia	333	366	-9	-8	13	15
Canada and Latin America	199	189	5	7	9	8
Total	2 484	2 420	3	5	100	100
<i>Of which in Established Markets</i>	1 823	1 749	4	7	73	72
<i>Of which in Emerging Growth Markets</i>	661	671	-1	0	27	28
Continuing operations						
Europe	4 492	4 231	6	11	37	38
US	4 380	3 664	20	20	36	33
Asia/Africa/Australasia	2 445	2 295	7	7	20	21
Canada and Latin America	855	826	4	9	7	8
Total	12 172	11 016	10	13	100	100
<i>Of which in Established Markets</i>	9 228	8 267	12	14	76	75
<i>Of which in Emerging Growth Markets</i>	2 944	2 749	7	10	24	25

¹ Net sales from operations by location of third-party customer. Emerging Growth Markets comprise all markets other than the Established Markets of the US, Canada, Western Europe, Japan, Australia and New Zealand.

² Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

Segmentation – Net sales by region¹ – Nine months to September 30

	9M 2019 USD m	9M 2018 USD m	% change		9M 2019 % of total	9M 2018 % of total
			USD	cc ²		
Innovative Medicines						
Europe	9 547	9 231	3	10	34	36
US	10 054	8 678	16	16	36	34
Asia/Africa/Australasia	6 235	5 978	4	7	22	23
Canada and Latin America	1 958	1 983	-1	9	8	7
Total	27 794	25 870	7	11	100	100
<i>Of which in Established Markets</i>	21 043	19 391	9	11	76	75
<i>Of which in Emerging Growth Markets</i>	6 751	6 479	4	12	24	25
Sandoz						
Europe	3 807	3 733	2	9	53	50
US	1 887	2 061	-8	-8	26	28
Asia/Africa/Australasia	984	1 030	-4	-1	14	14
Canada and Latin America	570	576	-1	5	7	8
Total	7 248	7 400	-2	2	100	100
<i>Of which in Established Markets</i>	5 314	5 417	-2	2	73	73
<i>Of which in Emerging Growth Markets</i>	1 934	1 983	-2	3	27	27
Continuing operations						
Europe	13 354	12 964	3	10	38	39
US	11 941	10 739	11	11	34	32
Asia/Africa/Australasia	7 219	7 008	3	6	21	21
Canada and Latin America	2 528	2 559	-1	8	7	8
Total	35 042	33 270	5	9	100	100
<i>Of which in Established Markets</i>	26 357	24 808	6	9	75	75
<i>Of which in Emerging Growth Markets</i>	8 685	8 462	3	10	25	25

¹ Net sales from operations by location of third-party customer. Emerging Growth Markets comprise all markets other than the Established Markets of the US, Canada, Western Europe, Japan, Australia and New Zealand.

² Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

Segmentation – Net sales by business franchise

Innovative Medicines net sales by business franchise – Third quarter

	Q3 2019 USD m	Q3 2018 USD m	% change USD	% change cc ³
Oncology				
<i>Tasigna</i>	487	444	10	11
<i>Sandostatin</i>	388	389	0	1
<i>Afinitor/Votubia</i>	400	374	7	8
<i>Promacta/Revolade</i>	380	295	29	31
<i>Tafinlar + Mekinist</i>	345	291	19	22
<i>Gleevec/Glivec</i>	320	380	-16	-14
<i>Jakavi</i>	279	248	13	17
<i>Exjade/Jadenu</i>	253	263	-4	-2
<i>Votrient</i>	198	197	1	2
<i>Lutathera</i>	119	56	113	116
<i>Kisqali</i>	123	72	71	76
<i>Kymriah</i>	79	20	295	295
<i>Piqray</i>	43		nm	nm
Other	301	276	9	11
Total Oncology business unit	3 715	3 305	12	14
Ophthalmology				
<i>Lucentis</i>	500	491	2	5
Travoprost Group	109	128	-15	-13
<i>Xiidra</i>	102		nm	nm
Other	503	475	6	7
Total Ophthalmology	1 214	1 094	11	13
Neuroscience				
<i>Gilenya</i>	829	818	1	3
<i>Zolgensma</i>	160		nm	nm
<i>Aimovig</i>	33		nm	nm
<i>Mayzent</i>	4		nm	nm
Other	16	20	-20	-21
Total Neuroscience	1 042	838	24	26
Immunology, Hepatology and Dermatology				
<i>Cosentyx</i>	937	750	25	27
<i>Ilaris</i>	177	141	26	27
Total Immunology, Hepatology and Dermatology	1 114	891	25	27
Respiratory				
<i>Ultibro Breezhaler</i>	97	110	-12	-8
<i>Seebri Breezhaler</i>	28	34	-18	-16
<i>Onbrez Breezhaler</i>	20	24	-17	-16
Subtotal COPD¹ portfolio	145	168	-14	-10
<i>Xolair²</i>	299	255	17	22
Other	4	6	-33	-21
Total Respiratory	448	429	4	9
Cardiovascular, Renal and Metabolism				
<i>Entresto</i>	430	271	59	61
Other	7	6	17	10
Total Cardiovascular, Renal and Metabolism	437	277	58	60
Established Medicines				
<i>Galvus Group</i>	320	307	4	5
<i>Diovan Group</i>	254	254	0	3
<i>Exforge Group</i>	249	253	-2	2
<i>Zortress/Certican</i>	122	120	2	5
<i>Neoral/Sandimmun(e)</i>	101	114	-11	-9
<i>Voltaren/Cataflam</i>	105	104	1	0
Other	567	610	-7	-5
Total Established Medicines	1 718	1 762	-2	0
Total Pharmaceuticals business unit	5 973	5 291	13	15
Total Division net sales	9 688	8 596	13	15

¹ Chronic Obstructive Pulmonary Disease

² *Xolair* sales for all indications are reported in the Respiratory franchise.

³ Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

nm = not meaningful

Innovative Medicines net sales by business franchise – Nine months to September 30

	9M 2019 USD m	9M 2018 USD m	% change USD	% change cc ³
Oncology				
<i>Tasigna</i>	1 389	1 398	-1	2
<i>Sandostatin</i>	1 183	1 188	0	2
<i>Afinitor/Votubia</i>	1 174	1 157	1	4
<i>Promacta/Revolade</i>	1 036	844	23	26
<i>Tafinlar + Mekinist</i>	982	842	17	22
<i>Gleevec/Glivec</i>	950	1 188	-20	-17
<i>Jakavi</i>	821	721	14	21
<i>Exjade/Jadenu</i>	744	813	-8	-6
<i>Votrient</i>	578	630	-8	-5
<i>Lutathera</i>	334	86	288	287
<i>Kisqali</i>	325	175	86	92
<i>Kymriah</i>	182	48	279	288
<i>Piqray</i>	49		nm	nm
Other	895	839	7	10
Total Oncology business unit	10 642	9 929	7	11
Ophthalmology				
<i>Lucentis</i>	1 569	1 526	3	8
Travoprost Group	330	386	-15	-12
<i>Xiidra</i>	102		nm	nm
Other	1 548	1 519	2	5
Total Ophthalmology	3 549	3 431	3	8
Neuroscience				
<i>Gilenya</i>	2 420	2 505	-3	0
<i>Zolgensma</i>	175		nm	nm
<i>Aimovig</i>	75		nm	nm
<i>Mayzent</i>	9		nm	nm
Other	46	63	-27	-24
Total Neuroscience	2 725	2 568	6	9
Immunology, Hepatology and Dermatology				
<i>Cosentyx</i>	2 586	2 031	27	30
<i>Ilaris</i>	493	399	24	28
Total Immunology, Hepatology and Dermatology	3 079	2 430	27	30
Respiratory				
<i>Ultibro Breezhaler</i>	313	332	-6	0
<i>Seebri Breezhaler</i>	93	111	-16	-11
<i>Onbrez Breezhaler</i>	62	78	-21	-15
Subtotal COPD¹ portfolio	468	521	-10	-5
<i>Xolair</i> ²	870	771	13	20
Other	16	19	-16	-6
Total Respiratory	1 354	1 311	3	10
Cardiovascular, Renal and Metabolism				
<i>Entresto</i>	1 208	710	70	75
Other	19	16	19	17
Total Cardiovascular, Renal and Metabolism	1 227	726	69	73
Established Medicines				
<i>Galvus Group</i>	955	957	0	5
<i>Diovan Group</i>	798	763	5	11
<i>Exforge Group</i>	780	751	4	10
<i>Zortress/Certican</i>	362	344	5	10
<i>Neoral/Sandimmun(e)</i>	314	349	-10	-6
<i>Voltaren/Cataflam</i>	313	333	-6	-3
Other	1 696	1 978	-14	-10
Total Established Medicines	5 218	5 475	-5	0
Total Pharmaceuticals business unit	17 152	15 941	8	12
Total Division net sales	27 794	25 870	7	11

¹ Chronic Obstructive Pulmonary Disease

² *Xolair* sales for all indications are reported in the Respiratory franchise.

³ Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

nm = not meaningful

Net sales of the top 20 Innovative Medicines products in 2019 – Third quarter

Brands	Business franchise	Key indication	US		Rest of world			Total		
			USD m	% change USD/cc ²	USD m	% change USD	% change cc ²	USD m	% change USD	% change cc ²
<i>Cosentyx</i>	Immunology, Hepatology and Dermatology	Psoriasis, ankylosing spondylitis and psoriatic arthritis	601	31	336	15	20	937	25	27
<i>Gilenya</i>	Neuroscience	Relapsing multiple sclerosis	469	7	360	-6	-1	829	1	3
<i>Lucentis</i>	Ophthalmology	Age-related macular degeneration			500	2	5	500	2	5
<i>Tasigna</i>	Oncology	Chronic myeloid leukemia	212	16	275	5	8	487	10	11
<i>Entresto</i>	Cardiovascular, Renal and Metabolism	Chronic heart failure	220	46	210	75	82	430	59	61
<i>Sandostatin</i>	Oncology	Carcinoid tumors and acromegaly	222	6	166	-8	-4	388	0	1
<i>Afinitor/Votubia</i>	Oncology	Breast cancer/TSC	266	18	134	-9	-7	400	7	8
<i>Promacta/Revolade</i>	Oncology	Immune thrombocytopenia (ITP), severe aplastic anemia (SAA)	188	31	192	26	31	380	29	31
<i>Tafinlar + Mekinist</i>	Oncology	BRAF V600+ metastatic and adjuvant melanoma; advanced non-small cell lung cancer (NSCLC)	126	8	219	26	31	345	19	22
<i>Galvus Group</i>	Established Medicines	Diabetes			320	4	5	320	4	5
<i>Gleevec/Glivec</i>	Oncology	Chronic myeloid leukemia and GIST	81	-26	239	-11	-9	320	-16	-14
<i>Xolair</i> ¹	Respiratory	Severe Allergic Asthma (SAA) and Chronic Spontaneous Urticaria (CSU)			299	17	22	299	17	22
<i>Jakavi</i>	Oncology	Myelofibrosis (MF), polycythemia vera (PV)			279	13	17	279	13	17
<i>Diovan Group</i>	Established Medicines	Hypertension	22	-15	232	2	5	254	0	3
<i>Exforge Group</i>	Established Medicines	Hypertension	5	0	244	-2	2	249	-2	2
<i>Exjade/Jadenu</i>	Oncology	Chronic iron overload	124	-3	129	-4	-1	253	-4	-2
<i>Votrient</i>	Oncology	Renal cell carcinoma	86	-9	112	9	11	198	1	2
<i>Ilaris</i>	Immunology, Hepatology and Dermatology	Auto-inflammatory (CAPS, TRAPS, HIDS/MKD, FMF, SJIA, AOSD and gout)	80	16	97	35	37	177	26	27
<i>Zortress/Certican</i>	Established Medicines	Transplantation	43	10	79	-2	2	122	2	5
<i>Lutathera</i>	Oncology	GEP-NETs gastroenteropancreatic neuroendocrine tumors	96	104	23	156	199	119	113	116
Top 20 products total			2 841	16	4 445	7	11	7 286	10	13
Rest of portfolio			884	58	1 518	5	8	2 402	20	22
Total division sales			3 725	24	5 963	7	10	9 688	13	15

¹ *Xolair* sales for all indications are reported in the Respiratory franchise.

² Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

Net sales of the top 20 Innovative Medicines products in 2019 – Nine months to September 30

Brands	Business franchise	Key indication	US		Rest of world			Total		
			USD m	% change USD/cc ²	USD m	% change USD	% change cc ²	USD m	% change USD	% change cc ²
<i>Cosentyx</i>	Immunology, Hepatology and Dermatology	Psoriasis, ankylosing spondylitis and psoriatic arthritis	1 609	36	977	16	23	2 586	27	30
<i>Gilenya</i>	Neuroscience	Relapsing multiple sclerosis	1 302	-1	1 118	-6	1	2 420	-3	0
<i>Lucentis</i>	Ophthalmology	Age-related macular degeneration			1 569	3	8	1 569	3	8
<i>Tasigna</i>	Oncology	Chronic myeloid leukemia	596	-1	793	-1	4	1 389	-1	2
<i>Entresto</i>	Cardiovascular, Renal and Metabolism	Chronic heart failure	640	65	568	77	87	1 208	70	75
<i>Sandostatin</i>	Oncology	Carcinoid tumors and acromegaly	655	7	528	-8	-2	1 183	0	2
<i>Afinitor/Votubia</i>	Oncology	Breast cancer/TSC	759	12	415	-13	-8	1 174	1	4
<i>Promacta/Revolade</i>	Oncology	Immune thrombocytopenia (ITP), severe aplastic anemia (SAA)	506	22	530	23	30	1 036	23	26
<i>Tafinlar + Mekinist</i>	Oncology	BRAF V600+ metastatic and adjuvant melanoma; advanced non-small cell lung cancer (NSCLC)	356	6	626	23	32	982	17	22
<i>Galvus Group</i>	Established Medicines	Diabetes			955	0	5	955	0	5
<i>Gleevec/Glivec</i>	Oncology	Chronic myeloid leukemia and GIST	256	-22	694	-19	-15	950	-20	-17
<i>Xolair</i> ¹	Respiratory	Severe Allergic Asthma (SAA) and Chronic Spontaneous Urticaria (CSU)			870	13	20	870	13	20
<i>Jakavi</i>	Oncology	Myelofibrosis (MF), polycythemia vera (PV)			821	14	21	821	14	21
<i>Diovan Group</i>	Established Medicines	Hypertension	67	0	731	5	12	798	5	11
<i>Exforge Group</i>	Established Medicines	Hypertension	12	-14	768	4	10	780	4	10
<i>Exjade/Jadenu</i>	Oncology	Chronic iron overload	355	-7	389	-10	-5	744	-8	-6
<i>Votrient</i>	Oncology	Renal cell carcinoma	258	-16	320	-1	5	578	-8	-5
<i>Ilaris</i>	Immunology, Hepatology and Dermatology	Auto-inflammatory (CAPS, TRAPS, HIDS/MKD, FMF, SJIA, AOSD and gout)	222	19	271	27	36	493	24	28
<i>Zortress/Certican</i>	Established Medicines	Transplantation	125	19	237	-1	6	362	5	10
<i>Lutathera</i>	Oncology	GEP-NETs gastroenteropancreatic neuroendocrine tumors	282	nm	52	174	182	334	288	287
Top 20 products total			8 000	14	13 232	5	11	21 232	8	12
Rest of portfolio			2 054	22	4 508	-1	4	6 562	5	9
Total division sales			10 054	16	17 740	3	9	27 794	7	11

¹ *Xolair* sales for all indications are reported in the Respiratory franchise.

² Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

Sandoz net sales by business franchise – Third quarter

	Q3 2019	Q3 2018	% change	% change
	USD m	USD m	USD	cc²
Retail Generics ¹	1 930	1 949	-1	1
Biopharmaceuticals	430	349	23	27
Anti-Infectives	124	122	2	5
Total Division net sales	2 484	2 420	3	5

¹ Of which USD 197 million (2018: USD 201 million) represents Anti-Infectives sold under Sandoz name

² Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

Sandoz net sales by business franchise – Nine months to September 30

	9M 2019	9M 2018	% change	% change
	USD m	USD m	USD	cc²
Retail Generics ¹	5 683	5 947	-4	0
Biopharmaceuticals	1 182	1 046	13	18
Anti-Infectives	383	407	-6	-2
Total Division net sales	7 248	7 400	-2	2

¹ Of which USD 587 million (2018: USD 618 million) represents Anti-Infectives sold under Sandoz name

² Constant currencies (cc) is a non-IFRS measure. A definition of non-IFRS measures used by Novartis can be found starting on page 56.

The product portfolio of Sandoz is widely spread in 2019 and 2018.

Segmentation – Other revenue – Third quarter

(USD millions)	Innovative Medicines		Sandoz		Corporate		Group	
	Q3 2019	Q3 2018	Q3 2019	Q3 2018	Q3 2019	Q3 2018	Q3 2019	Q3 2018
Profit sharing income	192	234	1	1			193	235
Royalty income	30	36	6	4	6	5	42	45
Milestone income	60	29		33			60	62
Other ¹	13				2		15	
Total other revenues	295	299	7	38	8	5	310	342

¹ Other includes revenue from activities such as manufacturing or other services rendered, to the extent such revenue is not recorded under net sales.

Segmentation – Other revenue – Nine months to September 30

(USD millions)	Innovative Medicines		Sandoz		Corporate		Group	
	9M 2019	9M 2018	9M 2019	9M 2018	9M 2019	9M 2018	9M 2019	9M 2018
Profit sharing income	542	564	2	2			544	566
Royalty income	79	121	13	7	19	16	111	144
Milestone income	158	107	23	36			181	143
Other ¹	27	15	3	3			30	18
Total other revenues	806	807	41	48	19	16	866	871

¹ Other includes revenue from activities such as manufacturing or other services rendered, to the extent such revenue is not recorded under net sales.

11. Discontinued operations

Consolidated income statement – Discontinued operations

(USD millions)	Q3 2019 ¹	Q3 2018	9M 2019	9M 2018
Net sales to third parties of discontinued operations	1 763	1 777	1 777	5 361
Sales to continuing segments			32	3
Net sales of discontinued operations	1 763	1 809	1 809	5 364
Cost of goods sold	-1 214	-860	-860	-3 073
Gross profit of discontinued operations	549	949	949	2 291
Selling, general and administration	-690	-638	-638	-2 027
Research and development	-132	-142	-142	-420
Other income	-7	15	15	74
Other expense	-20	-113	-113	-89
Operating income of discontinued operations	-300	71	71	-171
<i>as % of net sales</i>	<i>-17.0%</i>	<i>4.0%</i>	<i>4.0%</i>	<i>-3.2%</i>
Interest expense	-6	-10	-10	-19
Other financial income and expense	-2	-3	-3	-1
Income before taxes of discontinued operations	-308	58	58	-191
Taxes ²	50	-159	-159	31
Net loss from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders	-258	-101	-101	-160
Gain on distribution of Alcon Inc. to Novartis AG shareholders ³			4 691	
Net loss/income of discontinued operations	-258	4 590	4 590	-160

¹ As the Alcon spin-off was completed on April 9, 2019, there were no results of operations from the Alcon business recorded in Q3 2019.

² The tax rate on the net loss from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders of 274% was impacted by prior period items, which the Group has concluded is not material to the current period or the prior periods to which they related, and changes in uncertain tax positions. Excluding these items, the tax rate would have been 15.5%.

³ See Note 3 for further details on the gain on distribution of Alcon Inc. to Novartis AG shareholders.

The following are included in net income from discontinued operations:

(USD millions)	Q3 2019 ¹	Q3 2018	9M 2019	9M 2018
Interest income				1
Depreciation of property, plant and equipment	-61	-42	-42	-177
Amortization of intangible assets	-264	-174	-174	-794
Impairment charges on intangible assets	-350			-389
Additions to restructuring provisions				-4
Equity-based compensation of Novartis equity plans	-11	-9	-9	-34

¹ As the Alcon spin-off was completed on April 9, 2019, there were no results of operations from the Alcon business recorded in Q3 2019.

Supplemental cash flow disclosures related to the Alcon business distributed to Novartis AG shareholders

Net assets derecognized

(USD millions)

Property, plant and equipment	2 858
Right-of-use assets	269
Goodwill	8 906
Intangible assets other than goodwill	11 121
Deferred tax assets	732
Financial and other non-current assets	526
Inventories	1 469
Trade receivables and other current assets	1 787
Cash and cash equivalents	628
Deferred tax liabilities	-1 713
Current and non-current lease liabilities	-269
Current and non-current financial debts	-3 538
Trade payables, provisions and other liabilities	-2 751
Net assets derecognized	20 025

Net cash flows used in investing activities from discontinued operations

(USD millions)

	Q3 2019	9M 2019
Payments out of provisions for transaction costs attributable to the spin-off of the Alcon business	-12	-26
Divested cash and cash equivalents		-628
Cash flows attributable to the spin-off of the Alcon business	-12	-654
Other cash flows from/used in investing activities, net	15	-448
Net cash flows from/used in investing activities from discontinued operations	3	-1 102

Significant transaction closed in 2019 – Discontinued operations

In March 2019, Alcon acquired PowerVision, Inc. (PowerVision), a privately-held, US-based medical device development company focused on developing accommodative, implantable intraocular lenses. The fair value of the total purchase consideration was USD 424 million. The amount consisted of an initial cash payment of USD 289 million and the net present value of the contingent consideration of USD 135 million, due to PowerVision shareholders, which they are eligible to receive upon the achievement of specified regulatory and commercialization milestones. The preliminary purchase price allocation resulted in net identifiable assets of USD 418 million, consisting of intangible assets, of USD 505 million, net deferred tax liabilities of USD 93 million, other net assets of USD 6 million, and goodwill of USD 6 million. The 2019 results of operations since the date of the acquisition are not material.

For additional information related to the distribution (spin-off) of the Alcon business to Novartis AG shareholders, effected through a dividend in kind distribution that was completed on April 9, 2019, refer to Note 2 and 3.

SUPPLEMENTARY INFORMATION (unaudited)

Non-IFRS disclosures

Core results

The Group's core results – including core operating income, core net income and core earnings per share – exclude fully the amortization and impairment charges of intangible assets, excluding software, net gains and losses on fund investments and equity securities valued at fair value through profit and loss, and certain acquisition and divestment related items. The following items that exceed a threshold of USD 25 million are also excluded: integration and divestment related income and expenses, divestment gains and losses, restructuring charges/releases and related items, legal related items, impairments of property, plant and equipment and financial assets, as well as income and expense items that management deems exceptional and that are or are expected to accumulate within the year to be over a USD 25 million threshold.

Novartis believes that investor understanding of the Group's performance is enhanced by disclosing core measures of performance because, since they exclude items which can vary significantly from year to year, the core measures enable better comparison of business performance across years. For this same reason, Novartis uses these core measures in addition to IFRS and other measures as important factors in assessing the Group's performance.

The following are examples of how these core measures are utilized:

- In addition to monthly reports containing financial information prepared under International Financial Reporting Standards (IFRS), senior management receives a monthly analysis incorporating these core measures.
- Annual budgets are prepared for both IFRS and core measures.

Despite the use of these measures by management in setting goals and measuring the Group's performance, these are non-IFRS measures that have no standardized meaning prescribed by IFRS. As a result, such measures have limits in usefulness to investors.

Because of their non-standardized definitions, the core measures (unlike IFRS measures) may not be comparable to the calculation of similar measures of other companies. These core measures are presented solely to permit investors to more fully understand how the Group's management assesses underlying performance. These core measures are not, and should not be viewed as, a substitute for IFRS measures.

As an internal measure of Group performance, these core measures have limitations, and the Group's performance management process is not solely restricted to these metrics. A limitation of the core measures is that they provide a view of the Group's operations without including all events during a period, such as the effects of an acquisition, divestment, or amortization/impairments of purchased intangible assets and restructurings.

Constant currencies

Changes in the relative values of non-US currencies to the US dollar can affect the Group's financial results and financial position. To provide additional information that may be useful to investors, including changes in sales volume, we present information about our net sales and various values relating to operating and net income that are adjusted for such foreign currency effects.

Constant currency calculations have the goal of eliminating two exchange rate effects so that an estimate can be made of underlying changes in the consolidated income statement excluding the impact of fluctuations in exchange rates:

- the impact of translating the income statements of consolidated entities from their non-USD functional currencies to USD; and

- the impact of exchange rate movements on the major transactions of consolidated entities performed in currencies other than their functional currency.

We calculate constant currency measures by translating the current year's foreign currency values for sales and other income statement items into USD using the average exchange rates from the prior year and comparing them to the prior year values in USD.

We use these constant currency measures in evaluating the Group's performance, since they may assist us in evaluating our ongoing performance from year to year. However, in performing our evaluation, we also consider equivalent measures of performance which are not affected by changes in the relative value of currencies.

Growth rate calculation

For ease of understanding, Novartis uses a sign convention for its growth rates such that a reduction in operating expenses or losses compared to the prior year is shown as a positive growth.

Net debt and free cash flow

Net debt and free cash flow are non-IFRS financial measures, which means they should not be interpreted as measures determined under IFRS. Net debt is presented as additional information because management believes it is a useful supplemental indicator of the Group's ability to pay dividends, to meet financial commitments and to invest in new strategic opportunities, including strengthening its balance sheet. Free cash flow is presented as additional information because management believes it is a useful supplemental indicator of the Group's ability to operate without reliance on additional borrowing or use of existing cash. Free cash flow is a measure of the net cash generated that is available for debt repayment, investment in strategic opportunities and for returning to shareholders. Cash flows in connection with the acquisition or divestment of subsidiaries, associated companies and non-controlling interests in subsidiaries are not taken into account to determine free cash flow. Free cash flow is not intended to be a substitute measure for net cash flows from operating activities as determined under IFRS.

CORE RESULTS – Reconciliation from IFRS results to core results – Group – Third quarter

	Innovative Medicines		Sandoz		Corporate		Group	
(USD millions unless indicated otherwise)	Q3 2019	Q3 2018	Q3 2019	Q3 2018	Q3 2019	Q3 2018	Q3 2019	Q3 2018
IFRS operating income from continuing operations	2 404	2 184	191	358	-237	-303	2 358	2 239
Amortization of intangible assets	732	644	79	91			811	735
Impairments								
Intangible assets	13	50	32	110			45	160
Property, plant and equipment related to the Group-wide rationalization of manufacturing sites	44	1	62	5			106	6
Other property, plant and equipment		33						33
Total impairment charges	57	84	94	115			151	199
Acquisition or divestment of businesses and related items								
- Income	-2				-40	-3	-42	-3
- Expense	31	13			44	5	75	18
Total acquisition or divestment of businesses and related items, net	29	13			4	2	33	15
Other items								
Divestment gains	-6	-213				-10	-6	-223
Financial assets – fair value adjustments	-45	-44			16	41	-29	-3
Restructuring and related items								
- Income	-15	-3	-2		-3		-20	-3
- Expense	110	229	91	30	50	65	251	324
Legal-related items								
- Income		-1						-1
- Expense	31	11	72	60			103	71
Additional income		-8		-142	-83		-83	-150
Additional expense	3	1	90	29	86	25	179	55
Total other items	78	-28	251	-23	66	121	395	70
Total adjustments	896	713	424	183	70	123	1 390	1 019
Core operating income from continuing operations	3 300	2 897	615	541	-167	-180	3 748	3 258
<i>as % of net sales</i>	<i>34.1%</i>	<i>33.7%</i>	<i>24.8%</i>	<i>22.4%</i>			<i>30.8%</i>	<i>29.6%</i>
Income from associated companies			1	1	252	212	253	213
Core adjustments to income from associated companies, net of tax					60	80	60	80
Interest expense							-216	-229
Other financial income and expense							12	28
Core adjustments to other financial income and expense							-15	
Taxes, adjusted for above items (core taxes)							-630	-530
Core net income from continuing operations							3 212	2 820
Core net income from discontinued operations ¹								244
Core net income							3 212	3 064
Core net income attributable to shareholders of Novartis AG							3 213	3 063
Core basic EPS from continuing operations (USD)²							1.41	1.22
Core basic EPS from discontinued operations (USD) ²								0.10
Core basic EPS (USD)²							1.41	1.32

¹ For details on discontinued operations reconciliation from IFRS to core net income, please refer to page 68.

² Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

CORE RESULTS – Reconciliation from IFRS results to core results – Group – Nine months to September 30

	Innovative Medicines		Sandoz		Corporate		Group	
(USD millions unless indicated otherwise)	9M 2019	9M 2018	9M 2019	9M 2018	9M 2019	9M 2018	9M 2019	9M 2018
IFRS operating income from continuing operations	7 077	6 571	746	1 095	-560	-625	7 263	7 041
Amortization of intangible assets	1 710	1 680	239	283			1 949	1 963
Impairments								
Intangible assets	442	112	44	144			486	256
Property, plant and equipment related to the Group-wide rationalization of manufacturing sites	78	99	70	44			148	143
Other property, plant and equipment	1	42	6				7	42
Total impairment charges	521	253	120	188			641	441
Acquisition or divestment of businesses and related items								
- Income	-7				-79	-19	-86	-19
- Expense	57	99			83	27	140	126
Total acquisition or divestment of businesses and related items, net	50	99			4	8	54	107
Other items								
Divestment gains	-630	-490		-78	2	-55	-628	-623
Financial assets – fair value adjustments	-53	-122			4	73	-49	-49
Restructuring and related items								
- Income	-38	-11	-3	-2	-5	-2	-46	-15
- Expense	338	328	270	99	82	90	690	517
Legal-related items								
- Income		-1	-31	-63			-31	-64
- Expense	719	30	144	90			863	120
Additional income	-253	-38	-4	-142	-89		-346	-180
Additional expense	87	83	96	50	107	54	290	187
Total other items	170	-221	472	-46	101	160	743	-107
Total adjustments	2 451	1 811	831	425	105	168	3 387	2 404
Core operating income from continuing operations	9 528	8 382	1 577	1 520	-455	-457	10 650	9 445
<i>as % of net sales</i>	<i>34.3%</i>	<i>32.4%</i>	<i>21.8%</i>	<i>20.5%</i>			<i>30.4%</i>	<i>28.4%</i>
Income from associated companies	1		2	5	506	6 292	509	6 297
Core adjustments to income from associated companies, net of tax					335	-5 398	335	-5 398
Interest expense							-647	-684
Other financial income and expense							56	108
Core adjustments to other financial income and expense							5	
Taxes, adjusted for above items (core taxes)							-1 789	-1 529
Core net income from continuing operations							9 119	8 239
Core net income from discontinued operations ¹							278	818
Core net income							9 397	9 057
Core net income attributable to shareholders of Novartis AG							9 396	9 053
Core basic EPS from continuing operations (USD) ²							3.97	3.55
Core basic EPS from discontinued operations (USD) ²							0.12	0.35
Core basic EPS (USD) ²							4.09	3.90

¹ For details on discontinued operations reconciliation from IFRS to core net income, please refer to page 69.

² Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

CORE RESULTS – Reconciliation from IFRS results to core results – Group – Third quarter

(USD millions unless indicated otherwise)	Q3 2019 IFRS results	Amortization of intangible assets ¹	Impairments ²	Acquisition or divestment of businesses and related items ³	Other items ⁴	Q3 2019 Core results	Q3 2018 Core results
Gross profit from continuing operations	8 706	798	32	25	103	9 664	8 657
Operating income from continuing operations	2 358	811	151	33	395	3 748	3 258
Income before taxes from continuing operations	2 407	871	151	33	380	3 842	3 350
Taxes from continuing operations ⁵	-366					-630	-530
Net income from continuing operations	2 041					3 212	2 820
Net income from discontinued operations ⁶							244
Net income	2 041					3 212	3 064
Basic EPS from continuing operations (USD)⁷	0.90					1.41	1.22
Basic EPS from discontinued operations (USD) ⁷							0.10
Basic EPS (USD)⁷	0.90					1.41	1.32

The following are adjustments to arrive at core gross profit

Cost of goods sold	-3 776	798	32	25	103	-2 818	-2 729
--------------------	--------	-----	----	----	-----	--------	--------

The following are adjustments to arrive at core operating income

Selling, general and administration	-3 549			2	-15	-3 562	-3 246
Research and development	-2 199	13	13	-3	1	-2 175	-1 938
Other income	196			-42	-142	12	144
Other expense	-796		106	51	448	-191	-359

The following are adjustments to arrive at core income before taxes

Income from associated companies	253	60				313	293
Other financial income and expense	12				-15	-3	28

¹ Amortization of intangible assets: cost of goods sold includes amortization of acquired rights to in-market products and other production-related intangible assets; research and development includes the amortization of acquired rights for technologies; income from associated companies includes USD 60 million for the Novartis share of the estimated Roche core items

² Impairments: cost of goods sold and research and development include impairment charges related to intangible assets; other expense includes net impairment charges related to property, plant and equipment

³ Acquisition or divestment of businesses and related items, including restructuring and integration charges: cost of goods sold, selling, general and administration, research and development and other expense include net charges related to acquisitions; other income and other expense include transitional service-fee income and expenses, and other items related to the portfolio transformation and the Alcon spin-off

⁴ Other items: cost of goods sold and other expense include net restructuring and other charges related to the Group-wide rationalization of manufacturing sites; cost of goods sold, selling, general and administration, research and development, other income and other expense include other restructuring income and charges and related items; other income and other expense include fair value adjustments and divestment gains and losses on financial assets and environmental provisions; selling, general and administration also includes other provisions; other income also includes net gains from the divestment of products; other expense also includes legal-related items; other financial income and expense includes a revaluation impact of a financial liability incurred through the Alcon distribution

⁵ Taxes on the adjustments between IFRS and core results take into account, for each individual item included in the adjustment, the tax rate that will finally be applicable to the item based on the jurisdiction where the adjustment will finally have a tax impact. Generally, this results in amortization and impairment of intangible assets and acquisition-related restructuring and integration items having a full tax impact. There is usually a tax impact on other items, although this is not always the case for items arising from legal settlements in certain jurisdictions. Adjustments related to income from associated companies are recorded net of any related tax effect. Due to these factors and the differing effective tax rates in the various jurisdictions, the tax on the total adjustments of USD 1.4 billion to arrive at the core results before tax amounts to USD 264 million. The average tax rate on the adjustments is 18.4%, since the estimated quarterly core tax charge of 16.4% has been applied to the pre-tax income of the period.

⁶ For details on discontinued operations reconciliation from IFRS to core net income please refer to page 68.

⁷ Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

CORE RESULTS – Reconciliation from IFRS results to core results – Group – Nine months to September 30

(USD millions unless indicated otherwise)	9M 2019 IFRS results	Amortization of intangible assets ¹	Impairments ²	Acquisition or divestment of businesses and related items ³	Other items ⁴	9M 2019 Core results	9M 2018 Core results
Gross profit from continuing operations	25 528	1 914	44	25	202	27 713	25 887
Operating income from continuing operations	7 263	1 949	641	54	743	10 650	9 445
Income before taxes from continuing operations	7 181	2 284	641	54	748	10 908	9 768
Taxes from continuing operations ⁵	-1 163					-1 789	-1 529
Net income from continuing operations	6 018					9 119	8 239
Net income from discontinued operations ⁶	4 590					278	818
Net income	10 608					9 397	9 057
Basic EPS from continuing operations (USD)⁷	2.62					3.97	3.55
Basic EPS from discontinued operations (USD) ⁷	2.00					0.12	0.35
Basic EPS (USD)⁷	4.62					4.09	3.90

The following are adjustments to arrive at core gross profit

Other revenues	866				-66	800	871
Cost of goods sold	-10 433	1 914	44	25	268	-8 182	-8 315

The following are adjustments to arrive at core operating income

Selling, general and administration	-10 464			10	57	-10 397	-10 016
Research and development	-6 549	35	442	10	-131	-6 193	-5 978
Other income	1 388		-2	-86	-954	346	404
Other expense	-2 640		157	95	1 569	-819	-852

The following are adjustments to arrive at core income before taxes

Income from associated companies	509	335				844	899
Other financial income and expense	56				5	61	108

¹ Amortization of intangible assets: cost of goods sold includes amortization of acquired rights to in-market products and other production-related intangible assets; research and development includes the amortization of acquired rights for technologies; income from associated companies includes USD 335 million for the Novartis share of the estimated Roche core items

² Impairments: cost of goods sold and research and development include impairment charges related to intangible assets; research and development also includes the reversal of an impairment charge; other income and other expense include net impairment charges related to property, plant and equipment

³ Acquisition or divestment of businesses and related items, including restructuring and integration charges: cost of goods sold, selling, general and administration, research and development, other income and other expense include net charges related to acquisitions; other income and other expense also include transitional service fee income and expenses, and other items related to the portfolio transformation and the Alcon spin-off

⁴ Other items: other revenues includes a net income from an outlicensing agreement and an income related to an amendment of a collaboration agreement; cost of goods sold, other income and other expense include net restructuring and other charges related to the Group-wide rationalization of manufacturing sites; cost of goods sold, selling, general and administration, other income and other expense include other restructuring income and charges and related items; selling, general and administration also includes a receivable expected credit loss provision and other provisions; research and development also includes fair value adjustments of contingent consideration liabilities; other income also includes net gains from the divestment of products and property, plant & equipment and a provision release; other income and other expense also include fair value adjustments and divestment gains and losses on financial assets and legal-related items as well as environmental provisions; other expense also includes a provision for onerous contracts; other financial income and expense includes a revaluation impact of a financial liability incurred through the Alcon distribution

⁵ Taxes on the adjustments between IFRS and core results take into account, for each individual item included in the adjustment, the tax rate that will finally be applicable to the item based on the jurisdiction where the adjustment will finally have a tax impact. Generally, this results in amortization and impairment of intangible assets and acquisition-related restructuring and integration items having a full tax impact. There is usually a tax impact on other items, although this is not always the case for items arising from legal settlements in certain jurisdictions. Adjustments related to income from associated companies are recorded net of any related tax effect. Due to these factors and the differing effective tax rates in the various jurisdictions, the tax on the total adjustments for continuing operations of USD 3.7 billion to arrive at the core results before tax amounts to USD 626 million. The average tax rate on the adjustments is 16.8%, since the estimated full year core tax charge of 16.4% has been applied to the pre-tax income of the period.

⁶ For details on discontinued operations reconciliation from IFRS to core net income please refer to page 69.

⁷ Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

CORE RESULTS – Reconciliation from IFRS results to core results – Innovative Medicines – Third quarter

(USD millions)	Q3 2019 IFRS results	Amortization of intangible assets ¹	Impairments ²	Acquisition or divestment of businesses and related items ³	Other items ⁴	Q3 2019 Core results	Q3 2018 Core results
Gross profit	7 494	719		25	55	8 293	7 358
Operating income	2 404	732	57	29	78	3 300	2 897

The following are adjustments to arrive at core gross profit

Cost of goods sold	-2 679	719		25	55	-1 880	-1 743
--------------------	--------	-----	--	----	----	--------	--------

The following are adjustments to arrive at core operating income

Selling, general and administration	-2 868			2	-20	-2 886	-2 606
Research and development	-2 002	13	13	-3	1	-1 978	-1 742
Other income	86			-2	-67	17	64
Other expense	-306		44	7	109	-146	-177

¹ Amortization of intangible assets: cost of goods sold includes amortization of acquired rights to in-market products and other production-related intangible assets; research and development includes the amortization of acquired rights for technologies

² Impairments: research and development includes impairment charges related to intangible assets; other expense includes impairment charges related to property, plant and equipment

³ Acquisition or divestment of businesses and related items, including restructuring and integration charges: cost of goods sold, selling, general and administration, research and development and other expense include charges related to acquisitions; other income and other expense include transitional service-fee income and expenses related to the portfolio transformation and the Alcon spin-off

⁴ Other items: cost of goods sold and other expense include restructuring and other charges related to the Group-wide rationalization of manufacturing sites; cost of goods sold, selling, general and administration, research and development, other income and other expense include other restructuring income and charges and related items; other income and other expense include fair value adjustments on financial assets; other income also includes net gains from the divestment of products and financial assets; other expense includes legal-related items

CORE RESULTS – Reconciliation from IFRS results to core results – Innovative Medicines – Nine months to September 30

(USD millions)	9M 2019 IFRS results	Amortization of intangible assets ¹	Impairments ²	Acquisition or divestment of businesses and related items ³	Other items ⁴	9M 2019 Core results	9M 2018 Core results
Gross profit	21 986	1 675		25	78	23 764	21 981
Operating income	7 077	1 710	521	50	170	9 528	8 382

The following are adjustments to arrive at core gross profit

Other revenues	806				-66	740	807
Cost of goods sold	-7 230	1 675		25	144	-5 386	-5 247

The following are adjustments to arrive at core operating income

Selling, general and administration	-8 432			10	42	-8 380	-7 930
Research and development	-5 960	35	442	10	-131	-5 604	-5 388
Other income	1 008		-1	-7	-784	216	191
Other expense	-1 525		80	12	965	-468	-472

¹ Amortization of intangible assets: cost of goods sold includes amortization of acquired rights to in-market products and other production-related intangible assets; research and development includes the amortization of acquired rights for technologies

² Impairments: research and development includes impairment charges and a reversal of impairment charges related to intangible assets; other income and other expense include net impairment charges related to property, plant and equipment

³ Acquisition or divestment of businesses and related items, including restructuring and integration charges: cost of goods sold, selling, general and administration, research and development, other income and other expense include net charges related to acquisitions; other income and other expense also include transitional service-fee income and expenses related to the portfolio transformation and the Alcon spin-off

⁴ Other items: other revenues includes a net income from an outlicensing agreement and an income related to an amendment of a collaboration agreement; cost of goods sold, other income and other expense include restructuring and other charges related to the Group-wide rationalization of manufacturing sites; cost of goods sold, selling, general and administration, research and development, other income and other expense include other restructuring income and charges and related items; research and development also includes fair value adjustments of contingent consideration liabilities; other income and other expense include fair value adjustments on financial assets; other income also includes net gains from the divestment of property, plant and equipment, products and financial assets and provision releases; other expense includes legal-related items

CORE RESULTS – Reconciliation from IFRS results to core results – Sandoz – Third quarter

(USD millions)	Q3 2019 IFRS results	Amortization of intangible assets ¹	Impairments ²	Acquisition or divestment of businesses and related items	Other items ³	Q3 2019 Core results	Q3 2018 Core results
Gross profit	1 179	79	32		48	1 338	1 279
Operating income	191	79	94		251	615	541

The following are adjustments to arrive at core gross profit

Cost of goods sold	-1 354	79	32		48	-1 195	-1 228
--------------------	--------	----	----	--	----	--------	--------

The following are adjustments to arrive at core operating income

Selling, general and administration	-532				5	-527	-527
Other income	40				-2	38	44
Other expense	-299		62		200	-37	-59

¹ Amortization of intangible assets: cost of goods sold includes amortization of acquired rights to in-market products and other production-related intangible assets

² Impairments: cost of goods sold includes impairment charges related to intangible assets; other expense includes impairment charges related to property, plant and equipment

³ Other items: cost of goods sold and other expense include net restructuring and other charges related to the Group-wide rationalization of manufacturing sites; cost of goods sold, selling, general and administration, other income and other expense include restructuring income and charges and related items; selling, general and administration also includes other provisions; other expense includes legal-related items, an environmental provision and a provision for onerous contracts

CORE RESULTS – Reconciliation from IFRS results to core results – Sandoz – Nine months to September 30

(USD millions)	9M 2019 IFRS results	Amortization of intangible assets ¹	Impairments ²	Acquisition or divestment of businesses and related items	Other items ³	9M 2019 Core results	9M 2018 Core results
Gross profit	3 462	239	44		124	3 869	3 853
Operating income	746	239	120		472	1 577	1 520

The following are adjustments to arrive at core gross profit

Cost of goods sold	-3 945	239	44		124	-3 538	-3 735
--------------------	--------	-----	----	--	-----	--------	--------

The following are adjustments to arrive at core operating income

Selling, general and administration	-1 644				15	-1 629	-1 722
Other income	122		-1		-34	87	141
Other expense	-605		77		367	-161	-162

¹ Amortization of intangible assets: cost of goods sold includes amortization of acquired rights to in-market products and other production-related intangible assets

² Impairments: cost of goods sold includes impairment charges related to intangible assets; other income and other expense include net impairment charges related to property, plant and equipment

³ Other items: cost of goods sold and other expense include net restructuring and other charges related to the Group-wide rationalization of manufacturing sites; cost of goods sold, selling, general and administration, other income and other expense include restructuring income and charges and related items; selling, general and administration also includes a receivable expected credit loss provision and other provisions; other income and other expense include legal-related items; other expense also includes an environmental provision and a provision for onerous contracts

CORE RESULTS – Reconciliation from IFRS results to core results – Corporate continuing – Third quarter

(USD millions)	Q3 2019 IFRS results	Amortization of intangible assets ¹	Impairments	Acquisition or divestment of businesses and related items ²	Other items ³	Q3 2019 Core results	Q3 2018 Core results
Gross profit	33					33	20
Operating loss	-237			4	66	-167	-180

The following are adjustments to arrive at core operating income

Other income	70			-40	-73	-43	36
Other expense	-191			44	139	-8	-123

The following are adjustments to arrive at core income before taxes

Income from associated companies	252	60				312	292
Other financial income and expense	12				-15	-3	28

¹ Amortization of intangible assets: income from associated companies includes USD 60 million for the Novartis share of the estimated Roche core items

² Acquisition or divestment of businesses and related items, including restructuring and integration charges: other income and other expense include transitional service fee income and expenses, and other items related to the portfolio transformation and the Alcon spin-off

³ Other items: other income and other expense include fair value adjustments and divestment gains and losses on financial assets, restructuring charges and related items as well as environmental provisions; other financial income and expense includes a revaluation impact of a financial liability incurred through the Alcon distribution

CORE RESULTS – Reconciliation from IFRS results to core results – Corporate continuing – Nine months to September 30

(USD millions)	9M 2019 IFRS results	Amortization of intangible assets ¹	Impairments	Acquisition or divestment of businesses and related items ²	Other items ³	9M 2019 Core results	9M 2018 Core results
Gross profit	80					80	53
Operating loss	-560			4	101	-455	-457

The following are adjustments to arrive at core operating income

Other income	258			-79	-136	43	72
Other expense	-510			83	237	-190	-218

The following are adjustments to arrive at core income before taxes

Income from associated companies	506	335				841	894
Other financial income and expense	56				5	61	108

¹ Amortization of intangible assets: income from associated companies includes USD 335 million for the Novartis share of the estimated Roche core items

² Acquisition or divestment of businesses and related items, including restructuring and integration charges: other income and other expense include transitional service fee income and expenses, and other items related to the portfolio transformation and the Alcon spin-off

³ Other items: other income and other expense include fair value adjustments and divestment gains and losses on financial assets, restructuring income and charges and related items as well as environmental provisions; other financial income and expense includes a revaluation impact of a financial liability incurred through the Alcon distribution

CORE RESULTS – Reconciliation from IFRS results to core results – Discontinued operations – Third quarter

(USD millions)	Q3 2019 IFRS results	Amortization of intangible assets	Impairments	Acquisition or divestment of businesses and related items	Other items	Q3 2019 Core results	Q3 2018 Core results
Gross profit							1 124
Operating income of discontinued operations							297
Income before taxes of discontinued operations							289
Taxes							-45
Net income from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders							244
Net income from discontinued operations							244
Basic EPS (USD) ¹							0.10

¹ Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

CORE RESULTS – Reconciliation from IFRS results to core results – Discontinued operations – Nine months to September 30

(USD millions)	9M 2019 IFRS results	Amortization of intangible assets ¹	Impairments	Acquisition or divestment of businesses and related items ²	Other items ³	9M 2019 Core results	9M 2018 Core results
Gross profit	949	165			9	1 123	3 408
Operating income of discontinued operations	71	167			112	350	991
Income before taxes of discontinued operations	58					337	971
Taxes ⁴	-159					-59	-153
Net loss/income from discontinued operations before gain on distribution of Alcon Inc. to Novartis AG shareholders	-101					278	818
Gain on distribution of Alcon Inc. to Novartis AG shareholders	4 691			-4 691			
Net income from discontinued operations	4 590					278	818
Basic EPS (USD)⁵	2.00					0.12	0.35

The following are adjustments to arrive at core gross profit

Cost of goods sold	-860	165			9	-686	-1 956
--------------------	------	-----	--	--	---	------	--------

The following are adjustments to arrive at core operating income

Selling, general and administration	-638				14	-624	-2 027
Research and development	-142	2			4	-136	-384
Other income	15				-3	12	28
Other expense	-113				88	-25	-34

¹ Amortization of intangible assets: cost of goods sold includes amortization of acquired rights to in-market products and other production-related intangible assets; research and development includes the amortization of acquired rights for technologies

² Acquisition or divestment of businesses and related items represents the non-taxable non-cash gain adjustment related to the distribution of Alcon Inc. (spin-off) to Novartis AG shareholders

³ Other items: cost of goods sold, selling, general and administration, research and development and other expense include other restructuring charges and related items; research and development also includes amortization of option rights and the fair value adjustment of a contingent consideration liability; other income includes a fair value adjustments on a financial asset; other expense also includes legal-related items

⁴ Taxes on the adjustments between IFRS and core results take into account, for each individual item included in the adjustment, the tax rate that will finally be applicable to the item based on the jurisdiction where the adjustment will finally have a tax impact. Generally, this results in amortization and impairment of intangible assets and acquisition-related restructuring and integration items having a full tax impact. There is usually a tax impact on other items, although this is not always the case for items arising from legal settlements in certain jurisdictions. Due to these factors and the differing effective tax rates in the various jurisdictions, the tax on the total adjustments, excluding the non-taxable non-cash gain on the distribution (spin-off) of Alcon Inc. to Novartis AG shareholders of USD 279 million to arrive at the core results before tax amounts to USD 100 million. The 2019 core tax rate excluding the effect of the gain on distribution of Alcon Inc. to Novartis AG shareholders is 17.5%.

⁵ Earnings per share (EPS) is calculated on the amount of net income attributable to shareholders of Novartis AG.

Income from associated companies

(USD millions)	Q3 2019	Q3 2018	9M 2019	9M 2018
Share of estimated Roche reported results	283	250	695	621
Prior-year adjustment			-129	-125
Amortization of additional intangible assets recognized by Novartis on initial accounting for the equity interest	-30	-37	-99	-112
Partial release of deferred tax liability recognized			43	
Net income effect from Roche Holding AG	253	213	510	384
Share of estimated GSK Consumer Healthcare Holdings Ltd. reported results				119
Prior-year adjustment				4
Amortization of additional intangible assets recognized by Novartis on initial accounting for the equity interest				-3
Gain on divestment of GSK Consumer Healthcare Holdings Ltd., pre-tax ¹				5 791
Net income effect from GlaxoSmithKline Consumer Healthcare Holdings Ltd. ¹				5 911
Others			-1	2
Income from associated companies	253	213	509	6 297

¹ On March 27, 2018, Novartis entered into the agreement to divest its 36.5% investment in GSK Consumer Healthcare Holdings Ltd. to GSK. As a result, equity accounting was discontinued starting from April 1, 2018. The transaction closed on June 1, 2018, see Note 3.

Core income from associated companies

(USD millions)	Q3 2019	Q3 2018	9M 2019	9M 2018
Income from associated companies	253	213	509	6 297
Share of estimated Roche core adjustments	60	80	174	239
Roche prior year adjustment			161	133
Share of estimated GSK Consumer Healthcare Holdings Ltd. core adjustments ¹				20
GSK Consumer Healthcare Holdings Ltd. prior year adjustment				1
Gain on divestment of GSK Consumer Healthcare Holdings Ltd., pre-tax ¹				-5 791
Core income from associated companies	313	293	844	899

¹ On March 27, 2018, Novartis entered into the agreement to divest its 36.5% investment in GSK Consumer Healthcare Holdings Ltd. to GSK. As a result, equity accounting was discontinued starting from April 1, 2018. The transaction closed on June 1, 2018, see Note 3.

Condensed consolidated changes in net debt

Third quarter

(USD millions)	Q3 2019	Q3 2018
Change in cash and cash equivalents	-1 613	1 554
Change in marketable securities, commodities, financial debts and financial derivatives	68	584
Increase/reduction in net debt	-1 545	2 138
Net debt at July 1	-17 886	-19 210
Net debt at September 30	-19 431	-17 072

Nine months to September 30

(USD millions)	9M 2019	9M 2018
Change in cash and cash equivalents	-4 893	5 140
Change in marketable securities, commodities, financial debts and financial derivatives	1 646	-3 165
Increase/reduction in net debt	-3 247	1 975
Net debt at January 1	-16 184	-19 047
Net debt at September 30	-19 431	-17 072

Components of net debt

(USD millions)	Sep 30, 2019	Sep 30, 2018
Non-current financial debts	-20 131	-22 605
Current financial debts and derivative financial instruments	-8 017	-9 177
Total financial debt	-28 148	-31 782
Less liquidity:		
Cash and cash equivalents	8 378	14 000
Marketable securities, commodities, time deposits and derivative financial instruments	339	710
Total liquidity	8 717	14 710
Net debt at September 30	-19 431	-17 072

Share information

	Sep 30, 2019	Sep 30, 2018
Number of shares outstanding	2 264 608 111	2 309 972 655
Registered share price (CHF)	86.54	84.40
ADR price (USD)	86.90	86.16
Market capitalization (USD billions) ¹	197.5	199.6
Market capitalization (CHF billions) ¹	196.0	195.0

¹ Market capitalization is calculated based on the number of shares outstanding (excluding treasury shares). Market capitalization in USD is based on the market capitalization in CHF converted at the quarter end CHF/USD exchange rate.

Free cash flow

Third quarter

(USD millions)

	Q3 2019	Q3 2018	Change
Operating income from continuing operations	2 358	2 239	119
Adjustments for non-cash items			
Depreciation, amortization and impairments	1 373	1 422	-49
Change in provisions and other non-current liabilities	382	178	204
Other	199	-199	398
Operating income adjusted for non-cash items	4 312	3 640	672
Dividends received from associated companies and others	0	1	-1
Interest and other financial receipts	83	176	-93
Interest and other financial payments	-143	-181	38
Taxes paid	-235	-219	-16
Payments out of provisions and other net cash movements in non-current liabilities	-146	-208	62
Change in inventory and trade receivables less trade payables	17	-199	216
Change in other net current assets and other operating cash flow items	674	710	-36
Net cash flows from operating activities from continuing operations	4 562	3 720	842
Purchase of property, plant and equipment	-357	-295	-62
Proceeds from sales of property, plant and equipment	-3	4	-7
Purchase of intangible assets	-205	-546	341
Proceeds from sales of intangible assets	140	286	-146
Purchase of financial assets	-69	-77	8
Proceeds from sales of financial assets, net ¹	-91	74	-165
Purchase of other non-current assets	-10	-13	3
Proceeds from sales of other non-current assets	1	3	-2
Free cash flow from continuing operations	3 968	3 156	812
Free cash flow from discontinued operations		145	-145
Total free cash flow	3 968	3 301	667

¹ For the free cash flow, proceeds from the sales of financial assets excludes the cash inflows from the sale of a portion of the Alcon Inc. shares recognized by certain consolidated foundations through the Alcon spin-off, which amounted to USD 656 million. (see Note 3)

Free cash flow

Nine months to September 30

(USD millions)

	9M 2019	9M 2018	Change
Operating income from continuing operations	7 263	7 041	222
Adjustments for non-cash items			
Depreciation, amortization and impairments	3 840	3 526	314
Change in provisions and other non-current liabilities	1 400	425	975
Other	-113	-273	160
Operating income adjusted for non-cash items	12 390	10 719	1 671
Dividends received from associated companies and others	463	719	-256
Interest and other financial receipts	233	300	-67
Interest and other financial payments	-565	-567	2
Taxes paid	-1 195	-1 109	-86
Payments out of provisions and other net cash movements in non-current liabilities	-662	-472	-190
Change in inventory and trade receivables less trade payables	-1 289	-950	-339
Change in other net current assets and other operating cash flow items	632	973	-341
Net cash flows from operating activities from continuing operations	10 007	9 613	394
Purchase of property, plant and equipment	-918	-810	-108
Proceeds from sales of property, plant and equipment	809	55	754
Purchase of intangible assets	-703	-1 188	485
Proceeds from sales of intangible assets	421	702	-281
Purchase of financial assets	-223	-148	-75
Proceeds from sales of financial assets ¹	86	138	-52
Purchase of other non-current assets	-34	-26	-8
Proceeds from sales of other non-current assets	4	7	-3
Free cash flow from continuing operations	9 449	8 343	1 106
Free cash flow from discontinued operations	-62	435	-497
Total free cash flow	9 387	8 778	609

¹ For the free cash flow, proceeds from the sales of financial assets excludes the cash inflows from the sale of a portion of the Alcon Inc. shares recognized by certain consolidated foundations through the Alcon spin-off, which amounted to USD 656 million. (see Note 3)

Principal currency translation rates

Third quarter

(USD per unit)	Average rates Q3 2019	Average rates Q3 2018	Period-end rates Sep 30, 2019	Period-end rates Sep 30, 2018
1 CHF	1.014	1.017	1.008	1.024
1 CNY	0.143	0.147	0.140	0.145
1 EUR	1.112	1.163	1.094	1.163
1 GBP	1.232	1.303	1.229	1.307
100 JPY	0.932	0.897	0.927	0.882
100 RUB	1.548	1.525	1.546	1.523

Nine months to September 30

(USD per unit)	Average rates 9M 2019	Average rates 9M 2018	Period-end rates Sep 30, 2019	Period-end rates Sep 30, 2018
1 CHF	1.005	1.029	1.008	1.024
1 CNY	0.146	0.154	0.140	0.145
1 EUR	1.124	1.195	1.094	1.163
1 GBP	1.273	1.352	1.229	1.307
100 JPY	0.917	0.912	0.927	0.882
100 RUB	1.538	1.632	1.546	1.523

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995, that can generally be identified by words such as “guidance,” “launched,” “launching,” “strong start,” “momentum,” “growth investments,” “compelling,” “submissions,” “starting,” “submitted,” “submission,” “planned,” “focused,” “expected,” “to grow,” “continued,” “continuing,” “continue,” “potential,” “growing,” “launches,” “continues,” “expect,” “to be completed,” “pending,” “closing conditions,” “committed,” “growth drivers,” “launch,” “to date,” “ongoing,” “filings,” “Breakthrough Therapy Designation,” “delivering,” “will,” “plans,” “to submit,” “suggests,” “may,” “would,” “proposed,” “commitment,” “pipeline,” “priority,” “outlook,” “unforeseen,” “forecast,” “enter,” “to deliver,” “priority review,” “enrollment,” “filed,” “transformative,” “Orphan Drug designation,” “upcoming,” “on track,” “future,” “strategy,” “Fast Track designation,” “Orphan designation,” “Orphan status,” “resubmitted,” “potentially,” “anticipated,” “as early as possible,” “PRIME designation,” “Sakigake designation,” “underway,” “increasing,” “in the coming months,” or similar expressions, or by express or implied discussions regarding potential new products, potential new indications for existing products, potential product launches, or regarding potential future revenues from any such products; or regarding the potential outcome, or financial or other impact on Novartis, of the proposed divestiture of certain portions of our Sandoz Division business in the US; or regarding the potential impact of the completion of the up to USD 5 billion share buyback; or regarding potential future sales or earnings of the Group or any of its divisions or potential shareholder returns; or by discussions of strategy, plans, expectations or intentions. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. You should not place undue reliance on these statements. In particular, our expectations could be affected by, among other things: global trends toward healthcare cost containment, including ongoing government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; regulatory actions or delays or government regulation generally, including potential regulatory actions or delays with respect to the proposed transactions or the development of the products described in this press release; the potential that the proposed divestiture of certain portions of our Sandoz Division business in the US may not be completed in the expected time frame, or at all; the potential that the strategic benefits, synergies or opportunities expected from the proposed divestiture of certain portions of our Sandoz Division business in the US, and other transactions described, may not be realized or may be more difficult or take longer to realize than expected; the inherent uncertainties involved in predicting shareholder returns; the uncertainties inherent in the research and development of new healthcare products, including clinical trial results and additional analysis of existing clinical data; our ability to obtain or maintain proprietary intellectual property protection, including the ultimate extent of the impact on Novartis of the loss of patent protection and exclusivity on key products that commenced in prior years and will continue this year; safety, quality or manufacturing issues; uncertainties involved in the development or adoption of potentially transformational technologies and business models; uncertainties regarding actual or potential legal proceedings, including, among others, product liability litigation, disputes and litigation with business partners or business collaborators, government investigations generally, litigation and investigations regarding sales and marketing practices, and intellectual property disputes; our performance on environmental, social and governance measures; general political, economic and trade conditions, including uncertainties regarding the effects of ongoing instability in various parts of the world; uncertainties regarding future global exchange rates; uncertainties regarding future demand for our products; uncertainties regarding potential significant breaches of data security or data privacy, or disruptions of our information technology systems; and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements as a result of new information, future events or otherwise.

All product names appearing in italics are trademarks owned by or licensed to Novartis Group companies.

About Novartis

Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach more than 750 million people globally and we are finding innovative ways to expand access to our latest treatments. About 109,000 people of more than 140 nationalities work at Novartis around the world. Find out more at www.novartis.com

Novartis will conduct a conference call with investors to discuss this news release today at 14:00 Central European time and 8:00 Eastern Time. A simultaneous webcast of the call for investors and other interested parties may be accessed by visiting the Novartis website. A replay will be available after the live webcast by visiting.

<https://www.novartis.com/investors/event-calendar>

Information is provided on Novartis divisions and pipeline of selected compounds in late stage development and a copy of today's earnings call presentation can be found at.

<https://www.novartis.com/investors/event-calendar>

Important dates

December 5, 2019	R&D update 2019 – London
January 29, 2020	Fourth quarter and Full Year results 2019
April 28, 2020	First quarter results 2020
July 21, 2020	Second quarter results 2020
October 27, 2020	Third quarter results 2020

EXHIBIT 3

Home (L) > News (https://www.novartis.com/news) > [Sandoz Biologics License Application for proposed biosimilar denosumab accepted by US FDA](https://www.novartis.com/news/media-releases/sandoz-biologics-license-application-proposed-biosimilar-denosumab-accepted-us-fda) (https://www.novartis.com/news/media-releases/sandoz-biologics-license-application-proposed-biosimilar-denosumab-accepted-us-fda)

Sandoz Biologics License Application for proposed biosimilar denosumab accepted by US FDA

Feb 06, 2023

- *Submission supported by comprehensive analytical and clinical data package*
- *Denosumab indicated for treating variety of conditions including osteoporosis in postmenopausal women^{1,2}*
- *Sandoz continues to build biosimilars portfolio to increase patient access to high-quality therapies and support healthcare system sustainability*

Basel, February 06, 2023 — Sandoz, a global leader in off-patent (generic and biosimilar) medicines, today announced that the US Food and Drug Administration (FDA) has accepted its Biologics License Application (BLA) for proposed biosimilar denosumab.

The application includes all indications covered by the reference medicines Prolia[®] (denosumab)* and Xgeva[®] (denosumab)* for treating a variety of conditions, including osteoporosis in postmenopausal women and in men at increased risk of fractures, treatment-induced bone loss, prevention of skeletal related complications in cancer that has spread to the bone, giant cell tumor of the bone, and treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.^{1,2}

“In addition to being an important medicine for cancer of the bone, denosumab is critical in the treatment of osteoporosis and potential prevention of osteoporosis-related fractures that so many women over 50 are at risk of,” said Keren Haruvi, President, Sandoz Inc. and Head of North America.

“We are proud to be among the first to submit a BLA for a denosumab biosimilar as, if approved, it could increase patient access to an affordable, high-quality, potentially disease-modifying treatment across the US, while also delivering savings for healthcare systems.”

In the US alone, more than 10 million adults over age 50 are estimated to have osteoporosis, of whom more than 80% are women.³ It is predicted that one in two of these women and one in four men will have an osteoporosis-related fracture in their lifetimes.⁴ Osteoporosis-related fractures may lead to diminished quality of life, disability, and even death.⁵

The BLA includes a comprehensive analytical and clinical data package, including data from the Phase I/III ROSALIA study. Results confirmed that the proposed biosimilar denosumab matches the reference medicine in terms of pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity in women with postmenopausal osteoporosis; and contributes to demonstration of similarity, which is the basis for use in all indications.

Sandoz biosimilars help patients, in areas including immunology, oncology, supportive care and endocrinology, access critical and potentially life-changing medicines sustainably and affordably. Sandoz has a leading global portfolio with eight marketed biosimilars and a further 15-plus in various stages of development.

About denosumab

Denosumab is a human monoclonal antibody designed to bind to the RANKL protein, an activator of osteoclasts (cells involved in breaking down bone tissue).¹ By binding to and inhibiting RANKL, denosumab decreases the production and activity of osteoclasts, resulting in a reduction of bone loss, and subsequently the likelihood of fractures and other serious bone conditions.⁶

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,”

“expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that, if approved, such generic or biosimilar products will be approved for all indications included in the reference product’s label. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; the particular prescribing preferences of physicians and patients; competition in general, including potential approval of additional generic or biosimilar versions of such products; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; litigation outcomes, including intellectual property disputes or other legal efforts to prevent or limit Sandoz from selling its products; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

References

1. Amgen Inc. Prolia[®] (Denosumab): Prescribing Information. Available from:
https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Prolia/prolia_pi.pdf
(https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Prolia/prolia_pi.pdf) [Last accessed: January 2023].

2. Amgen Inc. Xgeva[®] (Denosumab): Prescribing Information. Available from:
https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/xgeva/xgeva_pi.pdf
(https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/xgeva/xgeva_pi.pdf) [Last accessed: January 2023].

3. Wright, N.C., et al., The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res, 2014. 29(11): p. 2520-6.

4. Cleveland Clinic Osteoporosis: Symptoms, Causes, Tests & Treatment (<https://my.clevelandclinic.org/health/diseases/4443-osteoporosis>). Available from: <https://my.clevelandclinic.org/health/diseases/4443-osteoporosis>
(<https://my.clevelandclinic.org/health/diseases/4443-osteoporosis>) [Last accessed: January 2023].

5. Osteoporosis and the Burden of Osteoporosis-Related Fractures. Available from:
https://www.ajmc.com/view/a357_11ma7__dempster_s164to169 (https://www.ajmc.com/view/a357_11ma7__dempster_s164to169) [Last accessed: January 2023].

6. International Osteoporosis Foundation. Facts and Statistics. Available from: <https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures> (<https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures>) [Last accessed: January 2023].

*Prolia[®] and Xgeva[®] are registered trademarks of Amgen Inc.

#

About Sandoz

Sandoz, a Novartis division, is a global leader in generic pharmaceuticals and biosimilars. Our purpose is to pioneer access for patients by developing and commercializing novel, affordable approaches that address unmet medical needs. Our ambition is to be the world’s leading and most valued generics company. Our broad portfolio of high-quality medicines, covering major therapeutic areas, accounted for 2022 sales of USD 9.2 billion.

Sandoz on social media:

LinkedIn: <https://www.linkedin.com/company/sandoz> (<https://www.linkedin.com/company/sandoz>)
Twitter: https://twitter.com/sandoz_global (https://twitter.com/sandoz_global)
Facebook: <https://www.facebook.com/sandozglobal/> (<https://www.facebook.com/sandozglobal/>)
Instagram: <https://www.instagram.com/sandozglobal> (<https://www.instagram.com/sandozglobal>)

###

Sandoz Global Communications

Central		North America	
Chris Lewis	+49 174 244 9501	Leslie Pott	+1 609 627 5287

Novartis Media Relations
E-mail: media.relations@novartis.com
(mailto:media.relations@novartis.com)

Central		North America	
Richard Jarvis	+41 79 584 2326	Julie Masow	+1 862 579 8456

Switzerland
Satoshi Sugimoto +41 79 619 2035

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com
(mailto:investor.relations@novartis.com)

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 345 4440
Nicole Zinsli-Somm	+41 61 324 3809	Parag Mahanti	+1 973 876 4912
Isabella Zinck	+41 61 324 7188		

[Musculoskeletal Diseases \(/tags/sub-category/musculoskeletal-diseases\)](/tags/sub-category/musculoskeletal-diseases)

[Cancer \(/tags/sub-category/cancer\)](/tags/sub-category/cancer)

 **Share**

 **Print (/node/461591/printable/print)**

 **Save (<https://ml-eu.globenewswire.com/Resource/Download/97409b05-0766-46e1-a2eb-3e803513b746>)**

EXHIBIT 4

[Home \(L\)](#) > [News \(https://www.novartis.com/news\)](https://www.novartis.com/news) > [Sandoz signs Memorandum of Understanding to build new biologics production plant in Slovenia, to support increasing global demand for biosimilar medicines \(https://www.novartis.com/news/media-releases/sandoz-signs-memorandum-understanding-build-new-biologics-production-plant-slovenia-support-increasing-global-demand-biosimilar-medicines\)](https://www.novartis.com/news/media-releases/sandoz-signs-memorandum-understanding-build-new-biologics-production-plant-slovenia-support-increasing-global-demand-biosimilar-medicines)

Sandoz signs Memorandum of Understanding to build new biologics production plant in Slovenia, to support increasing global demand for biosimilar medicines

Mar 09, 2023

- *Sandoz investment expected to be at least USD 400m – MOU signed today in Ljubljana at ceremony led by Slovenian Prime Minister and Sandoz CEO*
- *New project underpins Sandoz ambition to drive future growth of biosimilars, addressing increasing global demand*
- *One of largest-ever international private-sector investments in Slovenia, reinforces extensive Europe-wide Sandoz production network*

Basel, March 9, 2023 – Sandoz, a global leader in generic and biosimilar medicines, today signed a Memorandum of Understanding (MOU) to build a new biologics production plant in Lendava, Slovenia.

The Sandoz investment is expected to be at least USD 400 million, supporting the company’s ambition to drive the future growth of its global biosimilars portfolio. This represents one of the largest-ever international private-sector investments in Slovenia.

Speaking at the signing ceremony, Dr Robert Golob, Prime Minister of the Republic of Slovenia, said: “I am particularly pleased that this is an investment by a long-term strategic investor, a socially responsible and sustainable company, which is already one of the largest and most respected employers in Slovenia. With such investments, we are well on our way to a highly productive, competitive and green economy.”

Sandoz CEO Richard Saynor said: “Biosimilar medicines increase access to cutting-edge biologic therapies for the patients who need them most. At Sandoz, we are determined to continue leading the way on driving access to these critical medicines. This investment underscores our ambition to be the sustainable global leader in biosimilars, a segment projected to grow double-digit annually over the next decade.”


Glenn Gerecke, Global Head of Sandoz Technical Operations, added: “This state-of-the-art site will be a major new jewel in the Sandoz crown, enabling us to meet growing demand for our current and future biosimilars in the mid- to long-term. The location offers us a strong combination of political stability, proximity to our existing European-based production and commercial operations, and competitive costs.”

Work on the new plant is set to begin this year, with full operations provisionally planned for late 2026.

Sandoz also recently announced an additional EUR 50 million investment to expand its European-based antibiotics production network, bringing the total new investment commitment to the network in the past few years to EUR 250 million. Anti-infectives (primarily antibiotics) is the second largest Sandoz business after Biopharmaceuticals, and both have their roots in the company’s unique 75-year history of developing fermentation-based production technologies.

Sandoz is a pioneer and market leader in biosimilars and the leading global producer of generic antibiotics. The company is committed to building on its leadership role in these two critical and growing segments of the off-patent medicines market.

Disclaimer

 This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that, if approved, such generic or biosimilar products will be approved for all indications included in the reference product’s label. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; the particular prescribing preferences of physicians and patients; competition in general, including potential approval of additional generic or biosimilar versions of such products; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; litigation outcomes, including intellectual property disputes or other legal efforts to prevent or limit Sandoz from selling its products; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

#

About Sandoz

Sandoz, a Novartis division, is a global leader in generic pharmaceuticals and biosimilars. Our purpose is to pioneer access for patients by developing and commercializing novel, affordable approaches that address unmet medical needs. Our ambition is to be the world’s leading and most valued generics company. Our broad portfolio of high-quality medicines, covering major therapeutic areas, accounted for 2022 sales of USD 9.2 billion.

Sandoz on social media:

LinkedIn: <https://www.linkedin.com/company/sandoz> (<https://www.linkedin.com/company/sandoz>)
Twitter: https://twitter.com/sandoz_global (https://twitter.com/sandoz_global)
Facebook: <https://www.facebook.com/sandozglobal/> (<https://www.facebook.com/sandozglobal/>)
Instagram: <https://www.instagram.com/sandozglobal> (<https://www.instagram.com/sandozglobal>)

CEO Richard Saynor on LinkedIn: <https://www.linkedin.com/in/richard-saynor/> (<https://www.linkedin.com/in/richard-saynor/>)

#

Sandoz Global Communications

Central		North America	
Chris Lewis	+49 174 244 9501	Leslie Pott	+1 609 627 5287

Novartis Media Relations

E-mail: media.relations@novartis.com
(<mailto:media.relations@novartis.com>)

Central		North America	
Richard Jarvis	+41 79 584 2326	Julie Masow	+1 862 579 8456



+41 79 619 2035

Novartis Investor Relations

Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com
(mailto:investor.relations@novartis.com)

Central

North America

Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 345 4440
Nicole Zinsli-Somm	+41 61 324 3809	Parag Mahanti	+1 973 876 4912
Isabella Zinck	+41 61 324 7188		

Share

Print (/node/478191/printable/print)

Save (https://ml-eu.globenewswire.com/Resource/Download/a42d9324-a856-4646-8727-e6f796582b7b)

EXHIBIT 5



Sandoz Manufacturing



Manufacturing and expanding access to high-quality, more affordable biologics is critical to realizing Sandoz purpose to pioneer access for patients. Our expertise is grounded in more than 70 years of experience and we build on this every day by continually investing in the tools and infrastructure necessary to support quality and excellence in our biosimilar medicines.



Sandoz biosimilars and novel biologics share identical manufacturing standards.¹



Sandoz biosimilars are manufactured using the same state-of-the-art biological production technologies and quality standards as novel biologics.²



Biosimilar production is carried out on a clinical and commercial scale, using both microbial and cell-culture technologies.³



Each part of the manufacturing process is optimized so that it is capable of producing the same molecular structure as the originator product.⁴



This rigorous and comprehensive approach establishes comparability results in the production of biosimilars that are highly similar in potency, safety and purity, compared with their reference biologics.²



Sandoz biosimilar production takes place at clinical- and commercial-scale state-of-the-art facilities: Kundl and Schaftenau in Austria and Menges in Slovenia.^{3,5,6}

- Sandoz biosimilars and novel biologics share identical manufacturing standards.¹
- Sandoz biosimilars are manufactured using the same state-of-the-art biological production technologies and quality standards as novel biologics.²
- Biosimilar production is carried out on a clinical and commercial scale, using both microbial and cell-culture technologies.³
- Each part of the manufacturing process is optimized so that it is capable of producing the same molecular structure as the originator product.⁴

- This rigorous and comprehensive approach establishes comparability results in the production of biosimilars that are highly similar in potency, safety and purity, compared with their reference biologics.²
- Sandoz biosimilar production takes place at clinical- and commercial-scale state-of-the-art facilities: Kundl and Schafteu in Austria and Menges in Slovenia.^{3,5,6}

Go to Next Section:

Switching from a reference biologic to a biosimilar

<https://www.us.sandoz.com/our-work/biosimilars/switching-reference-biologic-biosimilar>

References: 1. Data on File. Manufacturing Manual version 2.0. Sandoz Inc. Princeton, NJ. 2. McCamish M, Woollett G. The state of the art in the development of biosimilars. Clin Pharmacol Ther. 2012;91:405-417. 3. Data on file. S-XBP-1335749. Sandoz Inc. Princeton, NJ. 4. McCamish M, Woollett G. Worldwide experience with biosimilar development. mAbs. 2011;3(2):209-217. doi:10.4161/mabs.3.2.15005. 5. ICIS. Contract biopharm manufacturing stays robust. <https://www.icis.com/resources/news/2004/01/16/549775/contract-biopharm-manufacturing-stays-robust>. Published January 16, 2004. Accessed October 7, 2020. 6. Sandoz. Sandoz Inaugurates Bioinject. <https://www.sandoz.com/news-media-releases/sandoz-inaugurates-bioinject-new-state-art-biopharmaceutical> – a new state-of-the-art biopharmaceutical manufacturing facility in Schafteu, Austria. Published September 17, 2015. Accessed October 7, 2020

Related Links

Biosimilar Development Process (</our-work/biosimilars/biosimilar-development-process>)

Extrapolation of Indications for Biosimilars

(</our-work/biosimilars/extrapolation-indications-biosimilars>)

Leadership (</our-work/biosimilars/leadership>)

Biosimilars and Access to Treatment (</our-work/biosimilars/biosimilars-and-access-treatment>)

© 2023 Sandoz AGThis site is intended for a US audience

[Terms of Use](#) | [Privacy Policy](#) | [About Cookies](#) | [Legal Notice](#)

EXHIBIT 6

Home (/) > About Sandoz (https://www.sandoz.com/about-sandoz) > Locations (https://www.sandoz.com/about/locations)

Locations

Sandoz

▼

Austria

▼

Showing 7 results

Sandoz	
Kundl / Tirol	
<i>Sandoz GmbH</i>	
Biochemiestrasse 10	Phone: +43 5338 200 0
A-6250 Kundl / Tirol	Fax: +43 5338 200 460
AUSTRIA	www.sandoz.at (http://www.sandoz.at)
Biochemiestrasse 10	
A-6250 Kundl / Tirol	
Austria	
Langkampfen / Schaftenau	
<i>Sandoz GmbH, Plant Schaftenau</i>	
Biochemiestrasse 10	Phone: +43 5372 6996 0
A-6336 Langkampfen / Schaftenau	Fax: +43 5372 6996 10
AUSTRIA	www.sandoz.at (http://www.sandoz.at)
Biochemiestrasse 10	
A-6336 Langkampfen / Schaftenau	
Austria	
Unterach am Attersee	
<i>EBEWE Pharma Ges.m.b.H Nfg. KG</i>	
Mondseestrasse 11	Phone: +43 5338 200
A-4866 Unterach am Attersee	Fax: +43 5338 8123 11
AUSTRIA	www.sandoz.at (http://www.sandoz.at)
Mondseestrasse 11	
A-4866 Unterach am Attersee	
Austria	
<i>Sandoz GmbH</i>	
Mondseestrasse 11	Phone: +43 7665 8123 0
A-4866 Unterach am Attersee	Fax: +43 7665 8123 11
AUSTRIA	

Mondseestrasse 11
Sandoz (A) A Novartis Company
Kerschbühlstrasse 11
A-1020 Wien
Austria

Wien

Hexal Pharma GmbH

Jakov-Lind-Strasse 5,
Top 3.05
Jakov-Lind-Strasse 5,
Top 3.05
A-1020 Wien
Austria

Phone: +43 1 4869622
Fax: +43 1 4869622 5657

www.sandoz.at (<http://www.sandoz.at>)

1A Pharma GmbH

Jakov-Lind-Strasse 5,
Top 3.05
Jakov-Lind-Strasse 5,
Top 3.05
A-1020 Wien
Austria

Phone: +43 1 480 5603
Fax: +43 1 4805603 5103

www.1apharma.at (<http://www.1apharma.at>)

Sandoz GmbH - Commercial Operations Austria

Jakov-Lind-Strasse 5, Top 3.05
A-1020 Wien
AUSTRIA
Jakov-Lind-Strasse 5, Top 3.05
A-1020 Wien
Austria

Phone: +43 1 8665 90
Fax: +43 1 8665 6914

www.sandoz.at (<http://www.sandoz.at>)

EXHIBIT 7

Home (/) > About Sandoz (https://www.sandoz.com/about-sandoz) > Locations (https://www.sandoz.com/about/locations)

Locations

Sandoz

▼

Slovenia

▼

Showing 6 results

Sandoz

Lendava

Cistilna naprava Lendava d.o.o.

Lendavska cesta 30
Centiba
Lendavska cesta 30
Centiba
SI-9220 Lendava
Slovenia

Phone: +386 2 578 9576
Fax: +386 2 577 3333

Lek Pharmaceuticals d.d., Lendava Site

Trimlini 2d
SI-9220 Lendava
SLOVENIA
Trimlini 2d
SI-9220 Lendava
Slovenia

Phone: +386 2 577 3333
Fax: +386 2 578 1331
www.lek.si/eng (http://www.lek.si/eng)

Ljubljana

Lek Pharmaceuticals d.d.

Verovskova ulica 57
SI-1526 Ljubljana
SLOVENIA
Verovskova ulica 57
SI-1526 Ljubljana
Slovenia

Phone: +386 1 580 2111
Fax: +386 1 568 3517
www.lek.si/eng (http://www.lek.si/eng)

Sandoz Pharmaceuticals d.d.

Verovskova ulica 57
SI-1000 Ljubljana
SLOVENIA
Verovskova ulica 57
SI-1000 Ljubljana

Phone: +386 1 580 2111
Fax: +386 1 568 3517

Lek Pharmaceuticals d.d., Menges Site

Kolodvorska 27
SI-1234 Menges
SLOVENIA
Kolodvorska 27
SI-1234 Menges
Slovenia

Phone: +386 1 721 7299
Fax: +386 1 723 7244

www.lek.si/eng (http://www.lek.si/eng)

Prevalje

Lek Pharmaceuticals d.d., Prevalje Site

Perzonali 47
SI-2391 Prevalje
SLOVENIA
Perzonali 47
SI-2391 Prevalje
Slovenia

Phone: +386 2 824 6300
Fax: +386 2 823 1557

www.lek.si/eng (http://www.lek.si/eng)

EXHIBIT 8

[Home \(L\)](#) > [News \(https://www.novartis.com/news\)](https://www.novartis.com/news) > [Novartis announces intention to separate Sandoz business to create a standalone company by way of a 100% spin-off \(https://www.novartis.com/news/media-releases/novartis-announces-intention-separate-sandoz-business-create-standalone-company-way-100-spin\)](https://www.novartis.com/news/media-releases/novartis-announces-intention-separate-sandoz-business-create-standalone-company-way-100-spin)

Novartis announces intention to separate Sandoz business to create a standalone company by way of a 100% spin-off

Aug 25, 2022

Ad hoc announcement pursuant to Art. 53 LR

- *Sandoz strategic review concludes that a separation of Sandoz by way of a 100% spin-off is in the best interest of shareholders, creating the #1 European generics company and a global leader in biosimilars, and a more focused Novartis*
- *Planned 100% spin-off would allow Novartis shareholders to participate fully in the potential future upside of both Sandoz and Novartis Innovative Medicines*
- *Sandoz is planned to be incorporated in Switzerland and to be listed on the SIX Swiss Exchange, with an American Depositary Receipt (ADR) program in the US*
- *Transaction is expected to be generally tax neutral for Novartis and is subject to market conditions, tax rulings and opinions, final Board endorsement and shareholder approvals; with completion expected in H2 2023*

Basel, August 25, 2022 — Novartis today announced its intention to separate Sandoz, its generics and biosimilars division into a new publicly traded standalone company, by way of a 100% spin-off.

The spin-off aims to maximize shareholder value by creating the #1 European generics company¹ and a global leader in biosimilars, allowing Novartis shareholders to participate fully in the potential future upside for both Sandoz and Novartis Innovative Medicines.

For both the Innovative Medicines and Sandoz businesses, the spin-off would enable enhanced focus and the ability to pursue independent growth strategies. Sandoz is expected to deliver its next wave of growth based on the existing biosimilars pipeline of 15+ molecules, a strong and experienced management team and organization. Novartis aims to become a focused innovative medicines company with a stronger financial profile, and improved return on capital.

The standalone Sandoz would be headquartered in Switzerland and listed on the SIX Swiss Exchange, with an American Depositary Receipt (ADR) program in the US.

Joerg Reinhardt, Chair of the Board of Directors of Novartis, said: “Our strategic review examined all options for Sandoz and concluded that a 100% spin-off is in the best interest of shareholders. A spin-off would allow our shareholders to benefit from the potential future successes of a more focused Novartis and a standalone Sandoz, and would offer differentiated and clear investment theses for the individual businesses. Sandoz would become the publicly traded #1 European generics company and a global leader in biosimilars based in Switzerland.”

Vas Narasimhan M.D., CEO of Novartis, said: “For Novartis, the separation of Sandoz would further support our strategy of building a focused innovative medicines company, with depth in five core therapeutic areas, and strength in technology platforms. In addition, both companies would be able to focus on maximizing value creation for their shareholders by prioritizing capital and resource allocation, employing separate capital structure policies, and increasing management focus on their respective business needs.”

Novartis: Focused Innovative Medicines Company

Novartis will continue expanding its strong position in five core therapeutic areas (Hematology, Solid Tumors, Immunology, Neuroscience and Cardiovascular), strength in technology platforms (Gene Therapy, Cell Therapy, Radioligand Therapy, Targeted Protein Degradation

and xRNA), and a balanced geographic footprint. Novartis will also continue progressing the implementation of its new organizational structure and announced in April 2022, integrating the Pharmaceuticals and Oncology business units with separate US and international commercial organizations supported by a new Strategy & Growth function and Operations unit to increase focus, strengthen competitiveness and drive synergies. Novartis remains committed to its strong investment-grade credit rating and capital allocation priorities, including our growing (CHF) annual dividend.

Sandoz: #1 European Generics Company and a Global Leader in Biosimilars

Sandoz generated USD 9.6bn sales in 2021 sales and served 100+ markets globally with a strong presence in Europe as well as in the United States and Rest of World. Sandoz would leverage its strong brand and sustain its leading global position by continuing to invest in the key strategic areas of Biosimilars, Antibiotics and Generic Medicines.

As a standalone company, Sandoz would focus on its vision to deliver access to patients, leveraging the business' strengths and purpose-driven workforce. Sandoz would execute on a growth strategy with a focused approach to deploy resources efficiently and effectively, strengthen key platforms and deliver launch excellence. Following the proposed spin-off, Sandoz would target an investment grade credit rating, providing sufficient financial flexibility to deliver on its growth plans, invest in incremental growth opportunities, with a vision to deliver attractive dividends. An update on Sandoz's planned dividend policy will be provided in due course. Any Sandoz dividends would be incremental to Novartis dividends.

Additional Transaction Details

Completion of the proposed spin-off is subject to satisfaction of certain conditions, including consultation with works councils and employee representatives (as required), general market conditions, receipt of favorable tax rulings and opinions, final endorsement by the Board of Directors of Novartis AG and shareholder approval. There can be no assurance regarding the ultimate timing of the proposed transaction or that the transaction will be completed. Further details of the proposed spin-off, including the proposed distribution ratio, detailed timeline and the composition of the board of directors of Sandoz will be provided at a later date.

Conference call

Novartis will hold an investor and analyst webcast today at 16:00 CET

¹ Based on IQVIA gross sales for combined Generics and Biosimilars market, referring to March 2022

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "can," "will," "plan," "may," "could," "would," "expect," "anticipate," "seek," "look forward," "believe," "committed," "investigational," "pipeline," "launch," or similar terms, or by express or implied discussions regarding the potential completion of the proposed spin-off of Sandoz; regarding the future commercial performance of Novartis or of Sandoz; regarding any potential strategic benefits, synergies or opportunities as a result of the proposed spin-off; or by discussions of strategy, plans, expectations or intentions. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the proposed spin-off will be completed in the expected form or within the expected time frame or at all. Nor can there be any guarantee that Novartis or a separate Sandoz business will be able to realize any of the potential strategic benefits, synergies or opportunities as a result of these actions. Neither can there be any guarantee that shareholders will achieve any particular level of shareholder returns. Nor can there be any guarantee that the proposed spin-off of Sandoz will maximize value for shareholders, or that Novartis or any of its divisions, or a separate Sandoz business, will be commercially successful in the future, or achieve any particular credit rating or financial results. In particular, our expectations could be affected by, among other things: an unexpected failure to complete, or unexpected delays in completing, the necessary actions for the proposed spin-off, or to obtain the necessary approvals to complete these actions; the potential strategic benefits, synergies or opportunities expected from the proposed spin-off may not be realized or may take longer to realize than expected; regulatory actions or delays or government regulation generally; the inherent uncertainty in predicting shareholder returns; the successful separation of Sandoz from Novartis and the timing of such separation; potential adverse reactions to the proposed spin-off by customers, suppliers, strategic partners or key Sandoz personnel and potential difficulties in maintaining relationships with such persons; the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis is reimagining medicine to improve and extend people’s lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world’s top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 108,000 people of more than 140 nationalities work at Novartis around the world. Find out more at <https://www.novartis.com> (<https://www.novartis.com>).

Novartis is on Twitter. Sign up to follow @Novartis at <https://twitter.com/novartisnews> (<https://twitter.com/novartisnews>)
For Novartis multimedia content, please visit <https://www.novartis.com/news/media-library> (<https://www.novartis.com/news/media-library>)
For questions about the site or required registration, please contact media.relations@novartis.com (<mailto:media.relations@novartis.com>)

About Sandoz

Sandoz, a Novartis division, is a global leader in generic pharmaceuticals and biosimilars. Our purpose is to pioneer access for patients by developing and commercializing novel, affordable approaches that address unmet medical needs. Our ambition is to be the world’s leading and most valued generics company. Our broad portfolio of high-quality medicines, covering all major therapeutic areas, accounted for 2021 sales of USD 9.6 billion. Find out more at <https://www.sandoz.com> (<https://www.sandoz.com>).

#

Novartis Media Relations

E-mail: media.relations@novartis.com (<mailto:media.relations@novartis.com>)

Richard Jarvis	Jamie Bennett
Strategy & Financial Communications	US External Engagement
+ 41 79 584 2326	+1 862 217 3976
richard.jarvis@novartis.com (mailto:richard.jarvis@novartis.com)	jamie.bennett@novartis.com
	(mailto:jamie.bennett@novartis.com)

Novartis Investor Relations

Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com (<mailto:investor.relations@novartis.com>)

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 345 4440
Nicole Zinsli-Somm	+41 61 324 3809	Alina Levchuk	+1 862 778 3372
Isabella Zinck	+41 61 324 7188	Parag Mahanti	+1 973-876-4912

- [Reimagine Medicine \(/tags/sub-category/reimagine-medicine\)](/tags/sub-category/reimagine-medicine)
- [Ad Hoc \(/tags/sub-category/ad-hoc\)](/tags/sub-category/ad-hoc)

[Access to Healthcare \(/tags/sub-category/access-healthcare\)](/tags/sub-category/access-healthcare)

 **Share**

 **Print (/node/180366/printable/print)**

 **Save (<https://ml-eu.globenewswire.com/Resource/Download/64836f4e-bf3e-4298-9269-572e96d1b977>)**

EXHIBIT 9

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761045Orig1s000

Trade Name: Ziextenzo

Generic or Proper Name: pegfilgrastim-bmez injection

Sponsor: Sandoz Inc.
November 4, 2019

Indication: Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

CENTER FOR DRUG EVALUATION AND RESEARCH

761045Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	X
REMS	
Summary Review	X
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	X
Product Quality Review(s)	X
Non-Clinical Review(s)	X
Statistical Review(s)	X
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761045Orig1s000

APPROVAL LETTER



BLA 761045

BLA APPROVAL

Sandoz Inc.
Attention: Bijal Pandhi, Pharm.D
RA Associate Director, Regulatory Affairs, Biopharmaceuticals
100 College Road West
Princeton, NJ 08540-6604

Dear Dr. Pandhi:

Please refer to your biologics license application (BLA) dated August 27, 2015, received August 27, 2015 and your amendments, submitted under section 351(k) of the Public Health Service Act for Ziextenzo (pegfilgrastim-bmez) injection.

We acknowledge receipt of your resubmission dated February 27, 2019, which constituted a complete response to our June 24, 2016 action letter.

LICENSING

We have approved your BLA for Ziextenzo (pegfilgrastim-bmez) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Ziextenzo under your existing Department of Health and Human Services U.S. License No. 2003. Ziextenzo is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture G-CSF (b) (4) at Sandoz GmbH in Kundl, Austria and pegfilgrastim-bmez drug substance at Lek Pharmaceuticals d.d. (a Sandoz company) in Menges, Slovenia. The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4)

(b) (4) You may label your product with the proprietary name, Ziextenzo, and market it in 6 mg/0.6 mL injection.

DATING PERIOD

The dating period for Ziextenzo shall be 36 months from the date of manufacture when stored at 5 ± 3 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

BLA 761045

Page 2

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Ziextenzo to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Ziextenzo, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (Prescribing Information, Patient Package Insert and Instructions for Use) Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on **August 22, 2019**, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761045.**” Approval of this submission by FDA is not required before the labeling is used.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

BLA 761045

Page 3

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric assessments until 10/2025.

Your deferred assessments required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are a postmarketing requirement. The status of this postmarketing requirement must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This postmarketing requirement is referred to as:

- #3734-1 Submit pediatric assessments for Ziextenzo (pegfilgrastim-bmez) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Ziextenzo (pegfilgrastim-bmez) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

Final Report Submission: 10/2025

Submit the protocol(s) to your IND 109743, with a cross-reference letter to this BLA.

Reports of this/these required pediatric assessments must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

BLA 761045
Page 4

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Patient Package Insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.³ Information and Instructions for completing the form can be found at FDA.gov.⁴ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁵

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

³ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁵ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

BLA 761045

Page 5

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert
 - Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANN T FARRELL
11/04/2019 04:47:16 PM

EXHIBIT 10

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761045Orig1s000

OTHER REVIEW(S)

USE-RELATED RISK ANALYSIS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 31, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761045
Product Name and Strength:	LA-EP2006* Ziextenzo (pegfilgrastim-bmez) 6 mg/0.6 mL
Product Type:	Drug-Device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sandoz
Submission Date:	February 27, 2019, April 3, 2019, July 18, 2019, July 26, 2019, and August 22, 2019
OSE RCM #:	2015-2000-1 and 2019-815
DMEPA Primary Reviewer:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

* LA-EP2006 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name, Ziextenzo, and the nonproprietary name, pegfilgrastim-bmez, are conditionally approved only with approval of "LA-EP2006".

1 REASON FOR REVIEW

Sandoz submitted a response to Complete Response for LA-EP2006 on February 27, 2019. This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), Patient Information, and Instructions for Use (IFU) for LA-EP2006 (BLA 761045) for areas of vulnerability that could lead to medication errors. In addition, we evaluated the use-related risk analysis (URRA) and comparative analyses submitted by Sandoz April 3, 2019.

1.1 PRODUCT BACKGROUND & REGULATORY HISTORY

On August 27, 2015, Sandoz submitted 351(k) BLA 761045 seeking licensure for LA-EP2006 as a biosimilar to US-licensed Neulasta. LA-EP2006 is being proposed for the indication of decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. DMEPA completed a label and labeling review for this application on June 23, 2016.^a The review included recommendations for the PI, IFU, container label, and carton labeling.

The application received a Complete Response (CR) letter on June 24, 2016^b due to clinical pharmacology and product quality issues. The CR letter stated that FDA reserved comment on the proposed labeling (including the PI and carton and container labeling) until the application is otherwise adequate. Sandoz submitted a response to the CR letter for LA-EP2006 on February 27, 2019. The assessments, conclusions, and recommendations in this review reflect new information and analyses that were not considered in the June 23, 2016 review (see Appendix H).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A

^a Whaley, E. Label and Labeling Review for LA-EP2006 BLA 761045. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 23. RCM No.: 2015-2000.

^b CR Letter: https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af803f1285&_afRedirect=3339187150565817

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Information Requests	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The response to complete response submission included the proposed container label, carton labeling, Prescribing Information (PI), Patient Information, and Instructions for Use (IFU). Sandoz is pursuing only one of the indications of US-licensed Neulasta (to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia).

Based on our initial assessment of the materials submitted, we determined additional information was needed to complete our evaluation. On March 28, 2019 we sent an information request (IR), requesting the submission of a comprehensive use-related risk analysis and comparative analyses for our review. See Appendix F for complete information request communications. Our assessment of the URRAs, comparative analyses, and labeling is described in the sections that follow.

3.1 USE-RELATED RISK ASSESSMENT

We note that LA-EP2006 has the same intended users, use environments, dosing, route of administration, and storage requirements as US-licensed Neulasta (BLA 125031) for its febrile neutropenia indication.

The sponsor submitted a URRAs, which identified and evaluated the tasks involved in the use of the LA-EP2006 prefilled syringe (PFS), the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors.

We reviewed the URRAs for the proposed product. We did not identify any new or unique risks for the LA-EP2006 PFS as compared to the US-licensed Neulasta PFS, but note that users are not required to activate the needle guard manually which we view as acceptable as described below.

3.2 COMPARATIVE ANALYSES

Physical Comparison

LA-EP2006 is supplied as a single-dose, ungraduated PFS with an UltraSafe Passive™ needle guard. US-licensed Neulasta is supplied as a single-dose, ungraduated PFS with a manual needle guard and as a PFS for use with a delivery device, the OnPro kit. Both products are supplied in a carton containing one PFS. We note in the physical comparison that the LA-EP2006 PFS plunger

rod is light blue whereas the plunger rod in the US-licensed Neulasta PFS is dark blue. The LA-EP2006 PFS plunger rod is shorter (56.3 mm) and has a larger plunger head diameter (17.8 mm) as compared to the plunger rod and plunger head in the US-licensed Neulasta PFS (57.8 mm and 10 mm respectively). Additionally, LA-EP2006 PFS has a clear UltraSafe Passive needle guard while US-licensed Neulasta has a translucent blue UltraSafe Active needle guard. In this particular instance, our evaluation of the physical comparison determined the physical differences should not affect critical tasks therefore, these differences are acceptable.

Task Comparison

We note in the task comparison, that the critical tasks for LA-EP2006 align with the critical tasks for US-licensed Neulasta, with one exception that users of the US-licensed Neulasta PFS are required to activate the needle guard manually, whereas, the LA-EP2006 PFS has a passive needle guard which does not require manual activation. The passive needle guard activates automatically to cover the needle when the user releases the plunger after the injection has been given and the syringe removed from the injection site. The manual system requires an additional user step (i.e., the user slides the needle guard over the needle). We do not consider activation of the needle guard as a critical task, and therefore, we find these differences acceptable.

Labeling Comparison: Side-by-Side IFU Comparison

The LA-EP2006 IFU follows similar steps and injection technique as US-licensed Neulasta. However, we note the following differences:

- Like US-licensed Neulasta, the LA-EP2006 PFS does not have graduation marks, and therefore, doses less than 6 mg (0.6 mL) cannot be accurately measured or directly administered without manipulation of the PFS content or dose approximation. Due to the potential for dosing errors, direct administration to patients requiring doses less than 0.6 mL (6 mg) is not recommended. The Prescribing Information for US-licensed Neulasta states that the PFS is not intended for direct administration of the drug for doses less than 0.6 mL (6 mg) and we note that similar statements also appear in the proposed LA-EP2006 labeling. However, we recommend that information regarding dosing limitations of the PFS be conveyed in the IFU, which is consistent with the IFU of US-licensed Neulasta.
- The LA-EP2006 IFU does not list the buttocks as an injection site (see Figure D). The upper outer area of the buttocks is listed as an injection site for the reference product, US-licensed Neulasta. Therefore, we request that the sponsor clarifies and provides reasoning for the discrepancy between LA-EP2006 IFU and the US-licensed Neulasta.
- US-licensed Neulasta can be administered at either a 45° or 90° angle. However, Figure H in the LA-EP2006 IFU, which depicts the injection technique, shows an approximate 45° injection angle, and the text accompanying the figure does not state the injection angle. Therefore, we request that the sponsor clarifies and provides reasoning for the discrepancy between LA-EP2006 IFU and the US-licensed Neulasta. Additionally, we

recommend revising the IFU to include the injection angle that should be used to administer LA-EP2006.

- Additionally, we identified other aspects of the IFU that should be revised to add and/or relocate important information regarding the administration of LA-EP2006 to harmonize with the labeling for US-licensed Neulasta.

On July 12, 2019, we sent an IR to Sandoz to provide recommendations for the IFU (see Appendix F).

The Sponsor submitted a response to the IR and provided updated IFU on July 18, 2019 (see Appendix G). We consulted with PLT to review the IFU and provided additional recommendations in an IR sent to Sandoz on July 25, 2019 (see Appendix F). On July 26, 2019, Sandoz submitted updated labels and labeling, including an updated IFU. We had no additional comments or recommendations at that time.

Labeling Comparison: Carton and Container Labels

Our review of the comparison of the carton and container labels determined that differences identified in the comparative analysis of the carton and container labels were product-specific information (e.g., tradename and dress). As such, we find these differences acceptable.

However, from a medication error perspective, we identified several areas that may be improved to increase the readability and prominence of important information on the carton and container labels. On July 12, 2019, we sent an IR to Sandoz to provide recommendations for the container labels and carton labeling (see Appendix F).

3.3 LABELING: PRESCRIBING INFORMATION

We performed a risk assessment of the proposed PI to evaluate the potential for medication errors. In section 2.2 Administration, we note that the LA-EP2006 prefilled syringe should be allowed "to reach room temperature for a minimum of 15-30 minutes"; however, in the US-licensed Neulasta labeling, the time listed is 30 minutes (no range). Therefore, we requested the sponsor provide rationale for the difference. This request was sent in an IR to Sandoz on July 12, 2019 (see Appendix F). Sandoz submitted a response to the IR and provided updated labels and labeling (PI and PPI) on July 26, 2019 (see Appendix G).

4 CONCLUSION & RECOMMENDATIONS

Our review of the URRRA concluded that there were no new or unique risks when compared to US-licensed Neulasta. We also note that the intended user group, intended uses, and use environments for LA-EP2006 aligns with US-licensed Neulasta for the febrile neutropenia indication.

We determined that the sponsor does not need to submit a human factors validation study for our review at this time. Any changes to the URRRA would warrant further review.

Additionally, as a biosimilar, the proposed labeling for LA-EP2006 is, in relevant part, substantially the same as the labeling for US-licensed Neulasta regarding administration of doses less than 0.6 mL (6 mg). On August 22, 2019, Sandoz submitted updated labels and labeling (PI, PPI, IFU, container label, and carton labeling) to reflect FDA's "conditional acceptance" of the proprietary name "Ziextenzo" for BLA 761045 (see Appendix G). We have no additional recommendations at this time.

APPENDICES

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for LA-EP2006 that Sandoz submitted on February 27, 2019 and US-licensed Neulasta.

Table 2. Relevant Product Information for Udenyca and US-Licensed Neulasta		
Product Name	Ziextenzo	US-licensed Neulasta ^c
Initial Approval Date	N/A	January 31, 2002
Nonproprietary or Proper Name	Pegfilgrastim-bmez	Pegfilgrastim
Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Neulasta is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection	Injection
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Dose and Frequency	Cancer patients receiving myelosuppressive chemotherapy: <ul style="list-style-type: none"> • 6mg administered subcutaneously once per chemotherapy cycle. • Do not administer Ziextenzo between 14 days before and 24 hours after administration of cytotoxic chemotherapy. • Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1. 	Cancer patients receiving myelosuppressive chemotherapy: <ul style="list-style-type: none"> • 6 mg administered subcutaneously once per chemotherapy cycle. • Do not administer between 14 days before and 24 hours after cytotoxic chemotherapy. • Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1.

^c Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Apr 2019. [cited 2019 Oct 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125031s198lbl.pdf

	<p>The ZIEXTENZO prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of ZIEXTENZO less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.</p> <p>Table 1. Dosing of Ziextenzo for pediatric patients weighing less than 45 kg</p> <table border="1"> <thead> <tr> <th>Body weight</th><th>LA-EP2006 Dose</th><th>Volume to administer</th></tr> </thead> <tbody> <tr> <td>Less than 10kg*</td><td>See below*</td><td>See below*</td></tr> <tr> <td>10-20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr> <tr> <td>21-30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr> <tr> <td>31-44 kg</td><td>4 mg</td><td>0.4 mL</td></tr> </tbody> </table> <p>*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Ziextenzo</p>	Body weight	LA-EP2006 Dose	Volume to administer	Less than 10kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL	<p>Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome:</p> <ul style="list-style-type: none"> Give 6 mg subcutaneously for adult victims with body weight \geq 45 kg for two doses given two weeks apart; for pediatric patients weighing less than 45 kg, use weight-based dosing. <p>The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.</p> <p>Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg</p> <table border="1"> <thead> <tr> <th>Body weight</th><th>Neulasta Dose</th><th>Volume to administer</th></tr> </thead> <tbody> <tr> <td>Less than 10kg*</td><td>See below*</td><td>See below*</td></tr> <tr> <td>10-20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr> <tr> <td>21-30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr> <tr> <td>31-44 kg</td><td>4 mg</td><td>0.4 mL</td></tr> </tbody> </table> <p>*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta</p>	Body weight	Neulasta Dose	Volume to administer	Less than 10kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL
Body weight	LA-EP2006 Dose	Volume to administer																														
Less than 10kg*	See below*	See below*																														
10-20 kg	1.5 mg	0.15 mL																														
21-30 kg	2.5 mg	0.25 mL																														
31-44 kg	4 mg	0.4 mL																														
Body weight	Neulasta Dose	Volume to administer																														
Less than 10kg*	See below*	See below*																														
10-20 kg	1.5 mg	0.15 mL																														
21-30 kg	2.5 mg	0.25 mL																														
31-44 kg	4 mg	0.4 mL																														
How Supplied	<p>Ziextenzo injection is a clear, colorless to slightly yellowish solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim-bmez, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe Passive™ Needle Guard.</p>	<p>Neulasta is a clear, colorless, preservative-free solution available as single dose prefilled syringe with an UltraSafe® Needle Guard, containing 6 mg/0.6 mL of pegfilgrastim as well as an OnPro kit which contains 6 mg/0.6 mL solution in a single prefilled syringe</p>																														

	Ziextenzo is provided in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 61314-866-01).	co-packaged with the on-body Injector for Neulasta.
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 72 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.	Store refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 8, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, 'LA-EP2006' and 'Ziextenzo'. Our search identified 1 previous label and labeling review and we considered our previous recommendations to see if they are applicable for this current review.

Reviewer	Document Title	Application	Date	RCM No.
Whaley, E.	Ziextenzo (biosimilar to Neulasta) Label and Labeling Review	BLA 761045	2016 JUN 23	2015-2000

APPENDIX C. HUMAN FACTORS

We received the following Human Factors documents submitted by Sandoz on April 3, 2019, per our March 28, 2019 information request.

Use-Related Risk Analysis

[\\cdsesub1\evsprod\bla761045\0049\m1\us\111-information-amendment\usability-risk-assessment.pdf](#)

Comparative Analyses

[\\cdsesub1\evsprod\bla761045\0049\m1\us\111-information-amendment\comparative-analysis.pdf](#)

APPENDIX F. INFORMATION REQUESTS

March 14, 2019: Request for Samples^d

We refer to your Class 2 Resubmission for BLA 761045 submitted on February 27, 2019.

We request you send three (3) intent-to-market samples (syringes), as well as associated packaging (cartons, blister) to assist in completion of our review.

Response: On April 17, 2019, we received the requested sample syringes and packaging.

March 28, 2019: Request for a URRRA and Comparative Analyses

We refer to your response to complete response for BLA 761045 submitted on February 27, 2019.

We note you are proposing a 6 mg/0.6 mL single-dose prefilled syringe with UltraSafe Passive Needle Guard. However, you have not submitted a comprehensive risk analysis for your proposed product.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications (see Draft Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development).

Additionally, if models of the same or similar combination products exist, it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Submit your risk analysis and comparative analyses to the Agency for review under the BLA.

^d IR communication. <https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af804e3fb6>

Response: On April 3, 2019, Sandoz submitted the requested URRAs and Comparative Analyses. See Appendix C.^e

July 12, 2019: USPI, PPI, IFU, and Carton and Container Label Comments sent to Sandoz^f

On July 12, 2019, the Agency issued an information request that included the following DMEPA recommendations for the PI, IFU, carton labeling, and container label.

Prescribing Information

A. Dosage and Administration [Section 2]

1. Administration [Section 2.2]

- a. We note users are instructed to “allow the LA-EP2006 prefilled syringe to reach room temperature for a minimum of 15-30 minutes”; however, in the US-licensed Neulasta labeling, the time listed is 30 minutes (no range). Therefore, please clarify and provide rationale for the discrepancy between the LA-EP2006 PI and the US-licensed Neulasta PI.

Instructions for Use

A. Instructions for Use – General Comments

1. Overall, we recommend you incorporate all relevant information from the IFU for the reference product US-licensed Neulasta and present such information in a similar manner where appropriate.
2. In order to highlight important information and align with the with US-licensed Neulasta IFU, we recommend adding and/or revising the section headings as listed below and relocating sections of the IFU so that they appear in the following order:
 - 1) Guide to Parts (this is a new section heading)
 - 2) Storage of the LA-EP2006 Syringe
 - 3) Using the Prefilled Syringe (revised from “Important safety information”)
 - 4) Gather the supplies for the injection (revised from “Items you additionally need for your injection”)
 - 5) Preparing the LA-EP2006 prefilled syringe for use
 - 6) Prepare and clean the injection site (revised from “Subcutaneous Injection” and “The injection site”)
 - 7) How to use the LA-EP2006 prefilled syringe
 - 8) Disposal Instructions

Note that figures will need to be relabeled to accommodate the new order of information.

^e Response to IR. 2019 APR 3. [\cdsesub1\evsprod\bla761045\0049\m1\us\111-information-amendment\md-information-amendment-ir2.pdf](#)

^f IR Communication: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805047c0&_afRedirect=2400478461515238


B. Instructions for Use – Guide to Parts

1. We recommend adding “Guide to Parts” as the section heading.
2. To align with the US-licensed Neulasta IFU, we recommend deleting the current “IMPORTANT” statement and replacing it with the following statement so that it appears directly below the “Guide to Parts” heading:

Important Information: Read the Patient Information for important information you need to know about LA-EP2006 before using the Instructions for Use.
3. Consider removing the label “(b) (4)” from Figure A as this technical term may not be understood by patients and caretakers. Additionally, this term is not referenced in the remainder of the IFU.
4. To align with the US-licensed Neulasta IFU, relocate the “after use” image of the PFS (i.e., Figure E) to this section below Figure A. Figure A may serve as the “before use” image of the syringe; therefore, the current figure F may be deleted. Additionally, we recommend labeling both images as presented in the US-licensed Neulasta IFU.
5. To align with the US-licensed Neulasta IFU, we recommend adding ‘Important: The needle is covered by the gray needle cap before use’ below the image of the “before use” syringe.

C. Instructions for Use – Using the Prefilled Syringe

1. We recommend revising the section heading “(b) (4)” to read “Using the Prefilled Syringe.” We also recommend including the following statements in the order listed below to highlight important information, improve clarity, and to align with the US-licensed Neulasta IFU:
 - It is important not to try to inject yourself or someone else until you have been trained by your healthcare provider (b) (4). **Please read all the instructions before injecting. Each sealed blister contains one prefilled syringe. Each prefilled syringe contains 6 mg/0.6 mL of LA-EP2006 drug solution.**
 - **Make sure that the name LA-EP2006 appears on the carton and prefilled syringe labels.**
 - **Check the carton and prefilled syringe labels to make sure the dose strength is 6 mg/0.6 mL.**
 - **You should not inject a dose of LA-EP2006 to children weighing less than 45 kg from a LA-EP2006 prefilled syringe. A dose less than 0.6 mL cannot be accurately measured using the LA-EP2006 prefilled syringe.”**
 - **Do not use the LA-EP2006 prefilled syringe if the carton is opened or damaged. Do not open the outer carton until you are ready to use the LA-EP2006 prefilled syringe.**
 - **The needle cap on the prefilled syringe contains natural rubber (derived from latex). Do not handle the prefilled syringe if you are allergic to latex.**

- **Do not** use the LA-EP2006 prefilled syringe if the seal of the blister is broken, as it may not be safe for you to use.
- **Do not** use the LA-EP2006 prefilled syringe if it has been dropped with the needle cap removed. The prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe.
-  (b) (4).
- **Do not** shake the LA-EP2006 prefilled syringe.
- **Do not** attempt to activate the LA-EP2006 prefilled syringe prior to injection.
- Be careful not to touch the needle guard wings before use. By touching them, the needle guard may be activated too early.
- **Do not** remove the needle cap until just before you give the injection.
- The LA-EP2006 prefilled syringe cannot be re-used. Please dispose the used LA-EP2006 prefilled syringe immediately after use in a sharps container.

2. As currently presented, the “Keep LA-EP2006 and all medicines out of the reach of children” warning statement is included twice (under Important Safety Information and after Storage). We recommend deleting the first occurrence as this is duplicate information.

D. Instructions for Use – Gather the supplies for the injection

1. We recommend revising the section heading “Items you additionally need for your injection” to read “Gather the supplies for the injection”.

E. Instructions for Use – Preparing the LA-EP2006 prefilled syringe for use

1. We recommend revising the following statements and adding additional information in the order stated below to improve readability and clarity of this information:

Preparing the LA-EP2006 prefilled syringe for use



(b) (4)

DO NOT USE if:

- the liquid contains visible particles, or if the liquid is cloudy or discolored.
- it appears used or damaged.
- if the gray needle cap is missing or not securely attached.
- the expiration date printed on the label has passed.

In all cases, use a new prefilled syringe and call your healthcare provider.

F. Instructions for Use - Prepare and clean the injection site

1. We recommend deleting the “ (b) (4) ” heading and revising “The injection site” heading to read “Prepare and clean the injection site”.
2. We recommend revising the following statements and adding additional information in the order stated below to align with US-licensed Neulasta and to improve readability and clarity of this information:

Prepare and clean the injection site

(b) (4)

- Clean the injection site with an alcohol swab. Let the skin dry.
- Do not touch this area again before injecting.

- If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
 - Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.
3. We recommend labeling Figures C and D with the appropriate injection sites to correspond with the text provided.
 4. We note Figure D and the corresponding text, does not list the upper outer area of buttocks as an injection site. The upper outer area of the buttocks is listed as an injection site if a caregiver is administering the injection for the reference product, US-licensed Neulasta. Therefore, please clarify and provide reasoning for the discrepancy between the LA-EP2006 IFU and the US-licensed Neulasta IFU.

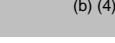
G. Instructions for Use - How to use the LA-EP2006 prefilled syringe

1. We recommend revising statements and adding additional information to the text that accompanies Figure G improve readability and highlight important information:

Figure G

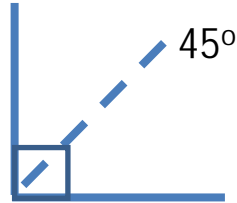


Hold the prefilled syringe by the syringe barrel. Carefully pull the needle cap straight off to remove it from the ~~ZIEXTENZO~~ prefilled syringe (see Figure G).

- Do not twist or bend the gray needle cap.
- Do not hold the prefilled syringe by the plunger rod.
-  (throw away) the needle cap in your household trash. You may see a drop of liquid at the end of the needle. This is normal.

2. The image used in Figure G does not match the accompanying text. The text states to “pull the needle cap straight off”, however, the image shows the needle cap is removed at an angle. Please revise the image used in Figure G to provide congruency with the text and the image. Further, we recommend adding language that instructs the user to hold the syringe barrel when removing the needle cap. As such, we recommend labeling the syringe barrel on the image.
3. Figure H shows the LA-EP2006 injection being given at an approximately 45° angle. However, US-licensed Neulasta can be administered at either a 45° or 90° angle. Therefore, please clarify and provide rationale for the discrepancy between LA-EP2006 and US-licensed Neulasta. Further, the accompanying text

does not mention at which angle the injection should be given. Therefore, revise the text to include the injection angle(s) that should be used to administer LA-EP2006. Additionally, include in the figure an additional image depicting the appropriate injection angle(s). For example:



4. The text accompanying Figure I states that [REDACTED] (b) (4) [REDACTED] " This step is not included in the US-licensed Neulasta IFU and this information was not identified as a difference in the task comparison section of the comparative analyses. Therefore, please clarify and provide rationale for the discrepancy between the LA-EP2006 PI and the US-licensed Neulasta PI.

RECOMMENDATIONS FOR SANDOZ

Container label (syringe label)

1. We note that the label contains a second perforated panel that includes the proprietary name, established name, lot number, and expiration date. Please confirm the intended use of this panel.
2. As currently presented, it is unclear whether the background color of the label is white or transparent. Please confirm the intended background color for the label.
3. Decrease the font size of the statement "Rx Only" and de-bold as this information appears more prominent than the nonproprietary name on the principal display panel.

Carton labeling (inner tray)

1. Revise the storage information statement to read "Store refrigerated at 2° to 8° C (36° to 46° F) in original carton to Protect from Light."
2. As currently presented, the location and format of the lot number and expiration date are not indicated. Please confirm the inclusion and location of these items.
 - a. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are

space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

3. Revise “Read full prescribing information before use” to read “Recommended Dosage: See prescribing information.” in accordance with 21 CFR 201.55.

Carton Labeling (outer)

1. As currently presented, the location and format of the lot number and expiration date are not indicated. Please confirm the inclusion and location of these items.
 - a. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2. As currently presented, the inclusion of a product identifier, including a 2D data matrix barcode, is not indicated. In September 2018, FDA released draft guidance, which, when finalized will represent the agency’s current thinking on the topics therein, on product identifiers required under the Drug Supply Chain Security Act.⁹ A product identifier is a standardized graphic that includes the product’s standardized numerical identifier (composed of the NDC and a unique alphanumeric serial number), lot number, and expiration date, in both human- and machine-readable formats. The product identifier data is specifically required under section 582(a)(9) of the FD&C Act to be in a “2-dimensional data matrix barcode” for packages and in a “linear or 2-dimensional data matrix barcode” for homogenous cases, which can be verified using “human-readable or machine-readable methods.” Section 582(b)(2)(A) of the FD&C Act requires manufacturers and repackagers, respectively, to “affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce”. Therefore, please confirm the inclusion and location of this information.

⁹ <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

3. We recommend removing storage information (i.e., Refrigerate. Do not freeze.) from the principal display panel as full storage information is stated on the back panel.
4. Revise the storage information statement on the back panel to read "Store refrigerated at 2° to 8° C (36° to 46° F) in original carton to Protect from Light."
5. The net quantity "1" appears with equal prominence to the product strength (i.e., 6 mg/0.6mL) which may increase the risk of numerical confusion. Therefore, we recommend spelling out the quantity "one" and decreasing the font size so that it is in alignment with the rest of the statement "Single-dose Prefilled Syringe with needle guard."
6. Increase the prominence of the route of administration "For Subcutaneous Use Only" to mitigate the risk of administration errors.
7. We recommend revising the preservative statement to read "Sterile solution – no preservative" to highlight this information.
8. Revise the usual dose statement, "Usual Dosage: See Prescribing Information" to read "Recommended Dosage: See prescribing information." in accordance with 21 CFR 201.55.

Response: On July 18, 2019, Sandoz submitted updated labels and labeling (PI, IFU, PPI, container label, and carton labeling). See Appendix G.^h

^h Response to IR. 2019 JUL 18. [\cdsesub1\evsprod\bla761045\0058\m1\us\12-cover-letters\cover-letter.pdf](#)

July 25, 2019: USPI, PPI, and IFU Comments Sent to Sandozⁱ

On July 25, 2019, the Agency issued an information request that included additional DMEPA recommendations for the IFU. The following recommendations include combined comments from DMEPA and PLT.



ⁱ IR Communication. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80507e24&_afRedirect=2400380567796728

APPENDIX H. ADDENDUM TO DMEPA REVIEW DATED JUNE 23, 2016

DMEPA completed a label and labeling review on June 23, 2016, for the biologics license application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act) seeking licensure for LA-EP2006. The assessments, conclusions, and recommendations in the current review reflect new information and analyses that were not available at the time of the June 2016 review. Accordingly, this addendum is intended to update the June 2016 review based on the new information and analyses now available. This addendum is also intended to clarify certain statements in the June 23, 2016 review regarding the Pediatric Research Equity Act (PREA) that are relevant here.

In particular, DMEPA considers the information and analysis in the following materials relevant to the topics addressed in its June 23, 2016, review, and incorporates them by reference here:

- October 4, 2019, DMEPA memorandum (archived to BLA 125031). On October 4, 2019, DMEPA finalized a memorandum of a comprehensive review and analysis of medication errors associated with doses of pegfilgrastim products less than 0.6 mL (6 mg) in pediatric patients. LA-EP2006 has the same strength, dosage form, and route of administration as US-licensed Neulasta, and, like US-licensed Neulasta, would only be available in a prefilled syringe without graduation marks. Additionally, the proposed labeling for LA-EP2006, in relevant part, is substantially the same as US-licensed Neulasta's labeling, including with respect to pediatric use information and the statements that the prefilled syringe is not designed to allow for direct administration and cannot accurately measure doses less than 0.6 mL (6 mg). Therefore, if the requirements for biosimilarity are met, LA-EP2006 would be expected to be associated with the same type of dosing error and potential consequences as US-licensed Neulasta. See also October 10, 2019, Memorandum on Requirements for Pediatric Assessments Pursuant to Section 505B(b)(1) of the FD&C Act.
- Order letter to sponsor of US-licensed Neulasta. On October 10, 2019, FDA issued an order letter pursuant to section 505B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to the sponsor of US-licensed Neulasta, requiring it to submit pediatric assessments as described in section 505B(a)(2)(A) of the FD&C Act. As described in the letter, the sponsor of U.S.-licensed Neulasta is subject to a postmarketing requirement referred to as submission of pediatric assessments for Neulasta (pegfilgrastim) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Neulasta (pegfilgrastim) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. In the letter, FDA stated it expected that a pediatric presentation – such as a vial or a pediatric-sized pre-filled syringe (with an appropriate concentration of product) – that can be used to directly and accurately deliver doses of less than 0.6 mL (6 mg) of pegfilgrastim to pediatric patients could be an "appropriate

formulation” as described in section 505B(a)(2)(A). (FDA issued similar letters to sponsors of the licensed pegfilgrastim biosimilars, Udenyca and Fulphila).

- Information request (IR) to Sandoz. An IR was sent to Sandoz on October 15, 2019, requesting its acknowledgement of a postmarketing requirement referred to as submit pediatric assessments for Ziextenzo (pegfilgrastim-bmez) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an “appropriate formulation” (presentation) that can be used to directly and accurately administer Ziextenzo (pegfilgrastim-bmez) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. DMEPA expects that fulfillment of Sandoz’s PMR would help mitigate the risk of pediatric dosing errors with LA-EP2006.

This addendum is also intended to clarify certain statements in the June 23, 2016 review regarding the Pediatric Research Equity Act (PREA) that are relevant here.

- PREA requires pediatric assessments for BLAs for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, unless the product is for an indication for which orphan designation has been granted (sections 505B(a)(1)(A) and 505B(k) of the FD&C Act). The required assessments “shall contain data, gathered using appropriate formulations for each age group for which the assessment is required” (section 505B(a)(2)(A) of the FD&C Act). FDA interprets this statutory text to include a presentation of the product that may be used to safely dose relevant pediatric patients. For additional information, see October 10, 2019, Memorandum on Requirements for Pediatric Assessments Pursuant to Section 505B(b)(1) of the FD&C Act.
- Based on FDA’s interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) and PREA, PREA requirements are applicable to proposed biosimilar products that have not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in: (1) a condition of use that has not been previously approved for the reference product; or (2) a dosage form, strength, or route of administration that differs from that of the reference product. For additional information, see FDA’s Draft Guidance for Industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Rev. 2) (Dec. 2018); when finalized, this guidance will represent the agency’s current thinking on the topics therein.

We carefully considered the June 23, 2016 review, together with the memoranda prepared subsequently, against the backdrop of the current framework for submitting pediatric assessments. We note that some of the statements and conclusions in the June 23, 2016 review are outdated. The more recent statements and conclusions based on additional data and

analyses apply here including with respect to medication errors, potential consequences, and appropriate means for addressing them.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEPHANIE L DEGRAW
10/31/2019 01:30:07 PM

HINA S MEHTA
10/31/2019 01:54:46 PM

QUYNHNHU T NGUYEN
11/01/2019 12:09:50 AM

MISHALE P MISTRY
11/01/2019 08:20:15 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY

OFFICE OF HEALTH TECHNOLOGY 3



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	7/1/2019		
To:	Rachel McMullen, Sr. Regulatory Health Program Manager; Laurel Menapace, Medical Officer		
Requesting Center/Office:	CDER/OHOP	Clinical Review Division:	Other
From:	David Wolloscheck, PhD OPEQ/OHT3/DHT3C		
Through (Team):	Sarah Mollo, PhD, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division): *optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: BLA 761045		
Recommendation:	Device Constituents Parts of the Combination Product are Approvable.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (optional)
David Wolloscheck -S <small>Digitally signed by David Wolloscheck -S Date: 2019.07.01 10:50:43 -04'00'</small>	Sarah Mollo <small>Digitally signed by Sarah Mollo DN: cn=Sarah Mollo, o=FDA, ou, email=sarah.mollo@fda.hhs.gov, c=US Date: 2019.07.01 14:17:32 -04'00'</small>	

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	00010374 and 0010391
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/500t000000IDXZvAAP/view
ICC tracking #	ICC1900279
Submission Number	BLA 761045
Sponsor	Sandoz
Drug/Biologic	La-EP2006
Indications for Use	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Device Constituent	Prefilled Syringe
Related Files	ICC1500591 (Device Review), ICC1500691 (Compliance)

2. CDRH REVIEW

ICC Review Request from CDER/OHOP, Other:	Laurel Menapace, Medical Officer
Device Presentation(s) being evaluated:	Prefilled Syringe
Objective of this Memo:	Evaluation of the following changes: Updates provided by Sandoz in Sections 3.2.P and 3.2.R and review compliance of manufacturing facility to relevant sections of 21 CFR 820
Review Comments:	See Background and Scope for additional information regarding the submission and objectives of this memo.
Review Recommendation:	Approvable

Background and Scope

BLA 761045 was submitted in August 27th, 2015 and has received a CR action on June 24th, 2016. CDER has requested a device review of the original submission and a review of the device constituent parts of the combination product was conducted by John McMichael (CDRH/ODE/DAGRID/GHDB). Mr. McMichael issued a final recommendation on February 17th, 2016 that the device constituent parts are approvable. In addition, a facilities review was conducted by Crystal Lewis (CDRH/OC/DMQ/REGO), which resulted in several deficiencies to the Sponsor due to a lack of documentation to show that the manufacturer of the final finished device complied with 21 CFR 820.20, .30, .50, and .100. The CR letter issued to Sandoz did not include any CDRH related issues. The Sponsor submitted a response to the CR action on February 27th, 2019. CDER requested a CDRH consult on April 10th, 2019 to review updates to sections 3.2.P and 3.2.R, as well as the applicant's compliance status for approvability.

Since the device was previously reviewed by CDRH and found approvable for the stated indications, this memo will only evaluate the updated sections and determine whether the additional information raises concerns regarding the

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

approvability of the device constituent parts of the combination product. The original device memo for this file will be attached to this document. In addition, a separate memo will review the provided information regarding the applicant's compliance to the relevant parts of 21 CFR 820.

Updates to Device Design Sections in 3.2.R

Sandoz provided a reviewer guide describing the individual changes that were made on each section in GSR 0048/1.2. Per the Sponsor, no content changes affecting the results of the activities or conclusions drawn thereof have been made. The changes made to the Device Design documentation in 3.2.R were summarized as follows:

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

(b) (4)

(b) (4)

(b) (4)

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Updated shelf-life of NSD

As stated in the original submission, Sandoz uses a 510(k) cleared needle safety device (NSD) (BD UltraSafe Passive Needle Guard, (b) (4)). The Sponsor has updated the shelf-life of the NSD from four to five years to align with the current shelf-life of the NSD per the manufacturer.

Comparative Human Factors Analysis between subject device and reference product

The Sponsor has also provided results of a Human Factors comparative analysis between the subject device and the US-licensed reference product Neulasta. In this comparative analysis, Sandoz conducted a physical comparison of the devices, as well as a comparison of the critical tasks and the labeling. The following table was provided for the physical and task comparison:

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

Table 6-4 Physical comparison of NG and plunger rod

Characteristic	Neulasta	LA-EP2006_PFS	(b) (4)
NG pre-activation appearance	(b) (4)		
NG post-activation appearance			
NG Length (A)	12.7 mm	12.7 mm	
NG Length (B)	62.0 mm	61.7 mm	
NG Length (C)	25.6 mm	25.4 mm	
NG color	Translucent blue	Clear	
NG mode of activation	Active – user has to activate the safety feature after injection	Passive – safety feature automatically activates at the end of stroke	
Plunger rod appearance	(b) (4)		
Plunger rod length (A)	57.8 mm	56.3 mm	
Plunger rod diameter (B)	10 mm	17.8 mm	
Plunger rod color	Dark blue	Light blue	

Table 6-5 Task analysis comparison of Neulasta and LA-EP2006_PFS

Tasks	Step	Neulasta	LA-EP2006_PFS_in	Difference
			(b) (4)	
Store	Store at 2-8°C.	X	X	Identical task
Unpack	Bring drug to room temperature.	X	X	Identical task
	Open packaging.	X	X	Identical task
	Remove product from packaging.	X	X	Identical task
	Perform safety checks (e.g. liquid appearance).	X	X	Identical task
Prepare injection	Identify appropriate injection site.	X	X	Identical task

v05.02.2019

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

Inject	Remove Rigid Needle Shield (RNS).	X	X	Identical task
	Pinch skin.	X	X	Identical task
	Insert needle into skin.	X	X	Identical task
	Depress plunger until the entire solution is injected.	X	X	Identical task
	Remove syringe from injection site.	X	X	Identical task
	Manually extend the NG to protect the needle.	X	N/A	Non-identical task; LA-EP2006_PFS_in (b) (4) comes with automatic NG that covers the needle preventing injuries and can be operated one-handed
Dispose	Dispose of device and packaging according to local regulations.	X	X	Identical task

The Sponsor stated that the main difference between the devices is the automated activation of the NSD in the subject device compared to a manual activation in the US-licenses Neulasta. The labeling of the two products was compared and found to only contain minor differences mainly due to the difference in the NSD. As the NSD has already received FDA clearance, the differences between the subject and the reference device are acceptable. The additional information does not raise new concerns regarding the usability of the subject device. Hence, this is acceptable.

Updates to Design Verification Section

Sandoz has updated the design verification section to include performance requirements of the NSD set by BD. The following table with performance requirements was provided:

Table 9-1 Performance requirements and specifications utilized by BD

Essential Performance Requirement	Specification	Verification
Activation force	Spring reaction force during activation all the way through the lockout	Pass
Triggering	Correct triggering along with full activation into locked position	Pass
Compression force	Force required to override the activated locked guard to the un-activated position	Pass
Essential Performance Requirement	Specification	Verification
Separation force	Force required to separate the guard from the body when the assembled device has been activated in its locked position	Pass
Syringe Spin test	Syringe spins freely at least in one direction	Pass

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

The device design verification of the NSD was already reviewed as part of the 510(k) (b) (4) Sandoz reported that the tested NSDs passed the verification testing. This is acceptable.

In addition to the performance requirements of the NSD, Sandoz also provided summary design verification data of the final finished combination product. The Sponsor noted that the additional data was, per FDA recommendations, generated with the intended drug product. Sandoz included additional performance requirements that were not previously reviewed by the original device reviewer. The following table with summary information was provided:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

Test	Description	Sample size [n]	Acceptance criteria	Result
movement test	that the syringe can freely rotate inside the safety device		must pass	
Needle guard test	Visual verification to ensure that the needle is completely covered by the needle guard after activation	100	All samples must pass	PASS
Flag label removability	Visual verification to ensure that the flag label on the syringe can be removed from the combination product	100	All samples but one must pass	PASS

The original device review evaluated dose accuracy/extractable volume and injection force (breakloose and glide force) and found that the provided data adequately addresses the performance requirements of the device constituent parts of the combination product. The acceptance criteria for these tests remain unchanged from the original submission. Furthermore, additional verification test data was leveraged in the original submission from the respective DMF. Since, the tested devices meet all of Sandoz's specifications and the Sponsor did not report any failures, the additional information provided does not raise new concerns regarding the performance of the prefilled syringe. Hence, the updates to this section are acceptable.

Control Strategy of Combination Product

The original review mentioned that dose accuracy testing was shown to be part of the Sponsor's lot release testing. However, the additional information provided on dose accuracy states that it is simply a release specification and not part of the release testing. The Sponsor justifies this by stating that the device performed adequately during design verification testing and after shipping validation. However, verification testing and shipping studies do not account for lot-to-lot variations. The Sponsor should demonstrate that an adequate control strategy is in place to account for variations between lots. Hence, an information request will be send to the Sponsor. See the end of this memo for details.

Additional Stability Data

Sandoz stated that the stability data in 3.2.P.8.1 was updated to include three batches from supplementary process validation from 2015 and one batch from 2016. The provided data will be evaluated to ensure that the provided data meets the predetermined acceptance criteria for the device constituent parts of the combination product.

Extractable Volume

The Sponsor provided additional data for extractable volume of 4 lots. The acceptance criterion for this test (b) (4) mL) remains unchanged from the original submission and was found adequate by the previous reviewer. The additional data provided meets the predetermined acceptance criterion and is acceptable.

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

Table 6-5 Results of extractable volume (mL) at intended storage condition of $5 \pm 3^\circ\text{C}$

Pull Point [months] / Batch	TR-10006	7004902	7004903	7004904	7007842	7007843	7007844	7008257
0	0.6	0.6	0.6	0.6	0.63	0.62	0.63	0.62
6	0.6	0.6	0.6	0.6	n.t.	n.t.	n.t.	n.t.
12	0.6	0.6	0.6	0.6	0.62	0.62	0.62	0.62
24	0.6	0.6	0.6	0.6	0.63	0.63	0.63	*
30	n.t.	0.624	0.622	0.624	n.t.	n.t.	n.t.	*
36	0.629	0.625	0.624	0.620	0.63	0.63	0.63	*

n.t. ... not tested

* Stability study still ongoing

Note:

(b) (4)

(b) (4) For the history of specifications please refer to (Module 3.2.P.5.4).

Stability data provided after accelerated aging:

Table 6-31 Results of extractable volume [mL] at accelerated storage condition of $25 \pm 2^\circ\text{C} / 60 \pm 5\% \text{ RH}$

Pull Point [months]	TR-10006	7004902	7004903	7004904	7007842	7007843	7007844	7008257
0	0.6	0.6	0.6	0.6	0.63	0.62	0.63	0.62
6	0.6	0.6	0.6	0.6	0.62	0.62	0.63	0.62

(b) (4)

Note:

history of specifications please refer to (Module 3.2.P.5.4).

For the

Breakloose and gliding force

The Sponsor stated that break-loose and glide force testing is not part of release and stability specifications. This was deemed acceptable to the original reviewer of the file. Sandoz stated that the syringes comply with ISO 7864, which describes the limit of breakloose and glide force as NMT 15 N. The additional data supplied for lot 7007843 shows a slightly higher breakloose force compared to lots that were previously tested. However, the reported results still demonstrate compliance with ISO 7864 and is acceptable.

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

Table 6-24 Results of break-loose and gliding force [N] at intended storage condition of $5 \pm 3^{\circ}\text{C}$

Pull Point [months]	7004902	7004903	7004904	7007843	7004902	7004903	7004904	7007843
	Break-loose (initial) force				Gliding (extrusion) force			
0	2.79	2.61	2.37	3.28	2.62	2.79	2.40	2.51
5	n.t.	n.t.	n.t.	3.33 ¹⁾	n.t.	n.t.	n.t.	2.64 ¹⁾
6	n.t.	n.t.	n.t.	3.45	n.t.	n.t.	n.t.	2.71
12	n.t.	n.t.	n.t.	4.03	n.t.	n.t.	n.t.	2.81
24	n.t.	n.t.	n.t.	4.44	n.t.	n.t.	n.t.	3.11
36	3.14	3.13	3.11	3.76	2.83	2.91	2.63	2.79
min.	2.79	2.61	2.37	3.28	2.62	2.79	2.40	2.51
max.	3.14	3.13	3.11	4.44	2.83	2.91	2.63	3.11
Δ	0.35	0.52	0.74	1.16	0.21	0.12	0.23	0.60

n.t. ...not tested

¹⁾ Samples mistakenly measured after 5 months additionally to the stability program. No negative impact expected as the results are shown as an additional pull point

No additional stability data of breakloose and glide force for devices that underwent accelerated aging was provided by the Sponsor. The reported results show that the additional lots tested are within the specifications set by the Sponsor and do not raise concerns regarding the approvability of the device constituent parts of the combination product.

---END OF REVIEW---

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

3. APPENDIX

3.1. DOCUMENTS REVIEWED

Sequence	Module
0000	3.2.R
0048	1.2, 1.11, 3.2.R

3.2. INTERACTIVE REVIEW

	Date Sent: 5/29/2019	Date/Sequence Received: 6/5/2019
Information Request #	<p>1. You stated in 3.2.R that dose accuracy is not part of release testing of the final combination product because results from design verification and transportation validation were acceptable. Please note that design verification or a shipping test do not account for variabilities between lots. As the manufacturer of the combination product, you should demonstrate that you have an adequate control strategy in place to account for lot-to-lot variabilities. Please add dose accuracy testing to your lot release testing. Alternatively, provide information on your control strategy to ensure that the essential performance requirements of the device constituent parts of your combination product are met throughout lot-to-lot variations.</p>	
Sponsor Response	<p>1.2 Sandoz Response</p> <p>Sandoz acknowledges the question raised by the Agency and would like to provide the justification for why we consider, in accordance with the control strategy, “extractable volume” release testing (b) (4) adequate and sufficient to ensure dose accuracy from the final combination product to the patient.</p> <p>1.2.1 Dose accuracy and extractable volume</p> <p>The combination product LA-EP2006_PFS (b) (4) consists of a prefilled syringe which is assembled with the BD UltraSafe Passive™ Needle Safety Device (NSD) (b) (4). The NSD consists of the needle guard assembly and the associated plunger rod. For LA-EP2006_PFS (b) (4) the entire volume is injected by manually pushing the plunger rod down until the end of the syringe. Hence, the dosing corresponds to expelling the entire syringe content while administering LA-EP2006 (i.e. “extractable volume”). As such, the relevant test in regards to “dose accuracy” is considered to be “extractable volume”. In accordance with the control</p>	

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

strategy, testing of the extractable volume

(b) (4)

as outlined below in Section 1.2.2.

Importantly, the extractable volume of LA-EP2006_PFS (b) (4) is not affected by the NSD since the NSD gets activated only once the plunger rod has been fully pushed down (i.e. once the full content of the PFS has been emptied).

This has been confirmed by Sandoz by specifically performing tests for extractable volume on fully assembled LA-EP2006_PFS (b) (4) in the course of our design verification process. In addition, the testing of extractable volume in the course of the transport validation also confirms that combination product samples going through the validated NSD assembly process and additional mechanical stress testing in the course of the transport validation, fulfill the specification for extractable volume. This leads to the conclusion that the assembly process and the transportation of LA-EP2006_PFS (b) (4) do not impact the extractable volume. This information has been provided in [Module 3.2.R Technical summary device parts]. We have provided a summary in Table 1-1 as well.

(b) (4)

(b) (4)

1.2.2 Extractable volume control strategy

(b) (4)

Sandoz

	<div data-bbox="1495 237 1539 260">(b) (4)</div>
	<p>1.2.4 Summary and conclusion</p> <p>With each injection of LA-EP2006_PFS (b) (4) the entire drug product volume is administered. Therefore “extractable volume” is the relevant test for “dose accuracy”. According to the control strategy, release and shelf-life specifications for extractable volume (b) (4). They account for LA-EP2006_PFS (b) (4) lot-to-lot variabilities since it was shown that the extractable volume is not impacted by neither the assembly of the NSD nor the NSD itself. Hence, Sandoz has an adequate control strategy in place to ensure that the specified volume is available for injection from LA- EP2006_PFS (b) (4)</p>
<p>Reviewer Comments</p>	<p>The Sponsor has clarified that the statement that release testing is not necessary pertains to the PFS with NSD (b) (4). This is acceptable, as the Sponsor has demonstrated that the impact of the NSD on expelled volume is minimal and the stability of the NSD was assessed as part of its 510(k) submission. Hence, the response is adequate.</p>
<p>Response Adequate:</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on <input type="text"/> Click or tap to enter a date.</p>

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	<input type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on Click or tap to enter a date.	



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum

CDER BLA 761045 - CDRH ICC1500591

Date: February 17, 2016

To: Rachel McMullen
Division of Hematology Products (DHP),
Office of Hematology and Oncology Products (OHOP),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: John McMichael,
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Through: CDR Alan Stevens, Acting Branch Chief,
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: Please review information submitted regarding the pre-filled syringe (PFS) drug presentation. PFS information for review is located in sections 3.2.P.7 and 3.2.R-Technical Summary Device Parts. Please also comment on instructions for use of the device located in section 1.14.1.3.

Documents Reviewed: Under GSR Sequence 0000: Technical Summary Device Parts under 3.2.R, Container closure system under 3.2.P.7

The following documents were reviewed upon receiving them as attachments via Information Request:

- LA-EP2006_PFS (b) (4) URS_2 – User Requirement Specification
- LA-EP2006_PFS (b) (4) DIR_2 – Design Input Requirements
- LA-EP2006 FDF mechanical stress Version 1.0 – Transport validation report
- Report: Physicochemical characterization of LA-EP2006 DP after transport validation
- LA-EP2006_PFS (b) (4) DVERPL_2 – Design Verification Plan
- LA-EP2006_PFS DVERP1_3 – Design Verification Test Protocol
- LA-EP2006_PFS DVERR1_1 – Design Verification Test Report
- LA-EP2006_PFS CLINEV_3 – Clinical Evaluation
- AIN457_CEV_PFS in SSI (b) (4) – Secukinumab Pre-Filled Safety Syringe Clinical Evaluation Report
- EP2006_PFS_30_48 (b) (4) CLINEV_3 – Clinical Evaluation Report
- LA-EP2006_PFS (b) (4) MUEP_2 – Risk Management and Usability Engineering Plan
- LISY-1mL-LA-EP2006_HID_2 – Hazard Identification

- LA-EP2006_PFS (b) (4) RA-AP1_2 – Application/Usability Risk Assessment
- FMEA LA-EP2006_RA-PR1_1 – Failure mode and effect analysis of the assembly and blistering process
- Response to Request for Information dated Jan. 20, 2016

CDRH Review Team:

Team Member	Role
John McMichael	Lead Reviewer – Engineering
Sarah Mollo, Ph.D.	Consultant – Biocompatibility
Steven Elliot	Consultant – Sterility

Recommendation: Device Constituent Parts of Combination Product are Approvable

I. Purpose

CDER/OND/OHOP/DHP has requested CDRH/ODE's assistance to assess the acceptability of the PFS with needle safety device presentation of the drug product. This is an original biosimilar BLA submission.

II. Background

Sandoz has submitted an original biosimilar BLA for "LA-EP2006" (pegfilgrastim, proposed biosimilar to US-licensed Neulasta). The proposed indication is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. This application will be part of a public Oncologic Drugs Advisory Committee (ODAC) Meeting. The scope of this review covers the device component of the combination product, which includes the pre-filled syringe, its device constituent parts, and the needle safety device.

III. Device Description (information taken from Section 4 of Technical Summary Device Parts under 3.2.R in GSR)

(b) (4) (b) (4) (b) (4)

(b) (4) (b) (4) (b) (4)

(b) (4)

(b) (4)

Intended Use/User Population:

(b) (4)

The combination product and its components are indicated for single use and the NG is indicated to aid in the protection of users from accidental sharps injuries.

The present marketing authorization application seeks licensure for all indications for which the US-licensed reference product Neulasta® is approved. Full information on the indications being applied for is provided in [Module 2.7.3].

Table 4-1 Intended user population: main characteristics

Category	Patients	Caregiver	Health Care Professional (HCP)
Age	Adults	Adults	Adults
Physical conditions	<ul style="list-style-type: none"> All stages of physical condition possible; No physical limitation due to the disease to be treated to be expected Needs to be judged "able to self-inject" by a HCP 	<ul style="list-style-type: none"> All stages of physical condition possible; Needs to be judged "able to inject" by a HCP 	<ul style="list-style-type: none"> All stages of physical condition possible (no limitations influencing the HCP's work to be expected).
Category	Patients	Caregiver	Health Care Professional (HCP)
Experience with similar devices	<ul style="list-style-type: none"> First time users Experienced users 	<ul style="list-style-type: none"> First time users Experienced users 	<ul style="list-style-type: none"> Experienced users

Operational Principles

The user pulls the needle cap straight off and inserts the needle into the skin. By pressing on the plunger rod he carries out the injection. Once the plunger head is completely located between the needle guard wings and the pressure on the plunger is released, the syringe spring is automatically activated and the NG extends and covers the exposed needle.

Drug Dose Capability

(b) (4)

Route of Administration/Injection Site

(b) (4)

(b) (4)

IV. Proposed Device Parts of the Combination Product (Information taken from Section 6 of Technical Summary of Device Parts under 3.2.R and Section 2 of Container closure system under 3.2.P.7)

Pre-filled Syringe:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Needle Safety Device:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

V. CDRH Review

This review is limited in scope to the design of the device parts of the combination product and does not pertain to the LA-EP2006 drug product itself, primary container closure elements, or the manufacturing of the device constituent part.

Performance Requirements

The following is a table of the essential performance requirements as stated by the Sponsor:

Essential Performance Requirement	Requirement / Specification
Dose Accuracy (Extractable Volume)	(b) (4)
Injection Depth / Needle Length	
Extrusion Force (break loose and glide force)	
Shelf Life	36 Months

Administrative

The following table was provided by the Sponsor in reference to the Letters of Authorization granting access to information held within suppliers' master files:

21 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL S MCMULLEN

02/19/2016

CDRH signed off on this ICC review memo on 2/17/16 and the Division received this on 2/19/16 from John McMichael (CDRH reviewer).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RACHEL S MCMULLEN
08/22/2019 04:47:56 PM

ICCR QUALITY SYSTEM REVIEW MEMO

Date: June 27, 2019

To: Laurel Menapace, Medical Officer, DHP/OHOP/OND, CDER, WO22, laurel.menapace@fda.hhs.gov

CC: Office of Combination Product, Combination@fda.hhs.gov
Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Rachel McMullen, DHP/OHOP/OND, CDER, WO22, Rachel.mcmullen@fda.hhs.gov

Through: CDR Nikhil Thakur, DHT3C/OHT3/OPEQ, CDRH, WO 66, Rm 2518, nikhil.thakur@fda.hhs.gov

From: David Wolloscheck, PhD, THT3C1/DHT3C/OHT3/OPEQ, CDRH, WO 66, Rm 2533, david.wolloscheck@fda.hhs.gov

Applicant/Licensure: Sandoz, Inc.
100 College Road West, Princeton, NJ 08540
3004828473

Submission (Type & Number): BLA 761045

Combination Product Name: La-EP2006

Combination Product Indications for Use: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Device Constituent (Type): Prefilled Syringe

ICCR Sharepoint Tracking Number: ICCR2019-04734

ICCR CTS Tracking Number: ICC1900294

Pre-Approval Facility Inspection: No

Documentation Review (Status): Complete

CDRH/OC Recommendation: Approvable

Instructions: Fill in fields shaded in gray or in brackets([]). Note: Brackets indicate repeated fields. Follow all instructions highlighted in gray and then delete it. In final version of this document, please make sure no text is highlighted in gray. If a section is not needed, please delete it. For example, if only one firm is involved in the manufacturing of the product, delete the second (combination product manufacturer) and third sites device constituent part manufacturer or specification developer).

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for BLA 761045 which will require a device inspection.

PRODUCT DESCRIPTION

The device constituent parts of BLA 761045 are a prefilled syringe and a needle safety device (NSD). The device is intended to be used by healthcare professionals (HCPs) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The NSD is indicated to aid in the protection of users from accidental needle injury. The following drawing of the devices was provided in the submission:

(b) (4)



REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the combination product, La-EP2006, in [BLA 761045](#).

Combination Product Applicant

Firm Name: Sandoz, Inc.

Address: 100 College Road West, Princeton, NJ 08540

FEI: 3004828473

Responsibility – As the applicant, Sandoz holds the primary responsibility that all manufacturing processes of the combination product are compliant with the applicable quality systems regulations. The applicant is using a drug CGMP based streamlined approach per the 2015 FDA guidance *Current Good Manufacturing Practice Requirements for Combination Products*.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted 2/22/2018 to 3/2/2018. The inspection covered drug CGMP and was classified VAI.

Inspection Recommendation:

An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Finished Combination Product Manufacturer



Responsibility – The firm is responsible for the manufacturing and packaging of the final finished combination product. Hence, it should comply with purchasing controls and CAPA. In addition, the firm is responsible for environmental monitoring and process controls.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered drug CGMP and was classified VAI.

Inspection Recommendation:

An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

DOCUMENTATION REVIEW

Device Constituent Part Type: Prefilled Syringe

Device Constituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, (b) (4)

Combination Product BLA 761045 Proposed Indication for Use: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

1. Was the last inspection of the finished combination product manufacturing site, (b) (4) OAI for drug or device observations?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	NA <input type="checkbox"/>
2. Is the device constituent a PMA or class III device?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
3. Is the final combination product meant for emergency use?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
5. Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>

cGMP Risk: ☒ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

Reviewer's Note:

The combination product is used by HCP in a clinical environment and is not intended for emergency use. Furthermore, the device is a prefilled syringe, which are generally considered low risk devices unless intended for emergency use (i.e. as part of an epinephrine emergency kit). Hence, an in-depth review of the Quality Systems of the combination product manufacturer is not needed.

However, due to a transition in the review practices, a previous review of the Quality Systems (QS) documentation was conducted and deficiencies were identified. The original reviewer noted that no information was found in the file regarding the documentation requirements set out in 21 CFR 820.20, .30, .50, and .100. In sequence 48 of the BLA, Sandoz has submitted a device amendment describing the Firm's adherence to these four parts of the QS. This information is reviewed as part of this memo.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant: Sandoz, Inc.
100 College Road West, Princeton, NJ 08540
FEI: 3004828473

Finished Combination
Product Manufacturer:



FEI: 3003813519

No Third Manufacturing

Site :

Applicable Sites Sandoz, Inc. <input checked="" type="checkbox"/>	Management Responsibility, 21 CFR 820.20 The firm provided a summary of how the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
(b) (4)	The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Applicable Sites Sandoz, Inc. <input checked="" type="checkbox"/>	Design Controls, General, 21 CFR 820.30 The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
(b) (4)	The firm provided a copy or a summary of the plan used to design the combination product.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Applicable Sites Sandoz, Inc. <input checked="" type="checkbox"/>	Purchasing Controls, 21 CFR 820.50 The sponsor firm should summarize its procedure(s) for purchasing controls.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
(b) (4)	The summary should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>

	The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Applicable Sites Sandoz, Inc. <input checked="" type="checkbox"/>	Corrective and Preventive Action (CAPA), 21 CFR 820.100 The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
(b) (4)	The CAPA system should require: a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
[Site3] <input type="checkbox"/>	b. Investigation of nonconformities and their causes;	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	d. Verification or validation of the actions taken.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Applicable Sites Sandoz, Inc. <input type="checkbox"/>	Installation, 21 CFR 820.170 (check none if Installation is not required for the combination product) If applicable for the combination product, the firm should provide a summary of how it has established installation, inspection instructions, and test procedures for the installation of the combination product.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
(b) (4)			
None: <input checked="" type="checkbox"/>			

<p>Applicable Sites</p> <p>Sandoz, Inc. <input type="checkbox"/></p> <p>(b) (4)</p> <p>None: <input checked="" type="checkbox"/></p>	<p>Servicing, 21 CFR 820.200 (check none if Servicing is not required for the combination product)</p> <p>Where servicing is a specified requirement for the combination product, the firm should provide a summary of how it has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.</p>	<p>YES <input type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p>Applicable Sites</p> <p>Sandoz, Inc. <input type="checkbox"/></p> <p>(b) (4)</p> <p>None: <input type="checkbox"/></p>	<p>Production and Process Controls</p> <p>The sponsor should provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.</p> <p>If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p>Applicable Sites</p> <p>Sandoz, Inc. <input type="checkbox"/></p> <p>(b) (4)</p> <p>None: <input type="checkbox"/></p>	<p>The sponsor should provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.</p> <p>If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>

Applicable Sites Sandoz, Inc. <input type="checkbox"/>	The sponsor should explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. The firm should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. The firm should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
<div style="background-color: #cccccc; height: 40px; width: 100%; text-align: center;">(b) (4)</div> None: <input type="checkbox"/>			

Reviewer's Note:

Sandoz provided responses to the information requests in 3.2.R – Device Quality System Information – Attachment 1. The Sponsor provided documentation describing the adherence to the four QS callouts for a combination product manufacturer operating under Drug cGMPs. The information was reviewed and found to be acceptable.

No Deficiencies Identified. The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable quality system requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The application for BLA 761045 La-EP2006 is approvable from the perspective of the applicable Quality System Requirements. The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

A routine surveillance inspection is recommended for the following facility to cover the device cGMP requirements:

a.

(b) (4)

OC Decision: Approvable (Recommend approval to CDER)

Reviewer: David Wolloscheck - S Digitally signed by David Wolloscheck -S
Date: 2019.06.27 17:02:07 -04'00'

Branch Chief or Lead CSO: Nikhil Thakur -S3 Digitally signed by Nikhil Thakur -S3
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nikhil Thakur -S3, 0.9.2342.19200300.100.1.1=1300215196
Date: 2019.06.28 00:24:28 -04'00'

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RACHEL S MCMULLEN
08/22/2019 04:45:04 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 26, 2019

TO: Ann T. Farrell, MD
Division Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDBE, OSIS

SUBJECT: Routine inspection of (b) (4)
supporting clinical study LA-EP06-104 (BLA 761045)

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an audit of Absolute Neutrophil Count (ANC) data for study LA-EP06-104 to support BLA 761045, conducted at (b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. However, ORA investigator Zerita White identified discrepancies in how ANC data were reported to the FDA.

2 Inspected Study:

BLA 761045

Study Number: LA-EP06-104

Study Title: "A randomized, double blind, crossover, three-way blinded study to compare the pharmacokinetics, pharmacodynamics, and safety of a single 6 mg subcutaneous administration of the proposed biosimilar product LA EP-2006, Neulasta US and Neulasta EU in healthy subjects"

Dates of conduct: (b) (4)

Analytical site: (b) (4)

ORA investigator Zerita White (b) (4) inspected (b) (4)
(b) (4) .

This is the first inspection of (b) (4) at this location. The inspection was initiated to review records of Absolute Neutrophil Count (ANC) data reported in study LA-EP06-104.

The clinical site generating blood samples for this portion of the study was PRA, Inc., of Lenexa, KS. During this inspection, Ms. White received documents provided by PRA to (b) (4), to assist in examination of the ANC records. However, there was no Form FDA 482-Notice of Inspection issued to PRA.

3 Inspectional Findings

During the inspection at (b) (4) Ms. White examined calibration and preventative maintenance records on all twelve Sysmex-XN-900 units used to perform Complete Blood Count (CBC) measurements, including ANC. Ms. White randomly selected twenty subjects to reconcile ANC results with the data listings submitted to FDA.

Ms. White compared the values in (b) (4) records to the ANC results submitted to the BLA. The BLA tabulations were labeled "Reported Concentration-ng/mL" (**ATTACHMENT 1**). When Ms. White started reviewing the data, the staff at (b) (4) informed Ms. White that this was a typographical error, and the actual units were "cells/ μ L." PRA provided an email statement that explained this error (**ATTACHMENT 2**).

Ms. White found no discrepancies in ANC results between (b) (4) records and the BLA report, using the screening and enrollment log provided by PRA to (b) (4) during the inspection (**ATTACHMENT 3**). The blood samples analyzed for ANC were labeled with the Screen ID of the enrolled subjects, instead of the randomization number. Therefore, to match the ANC results, (b) (4) records (**ATTACHMENT 4**) had to be matched with the randomization numbers in the screening and enrollment log provided by PRA to (b) (4) (**ATTACHMENTS 3**). For example, the Case Study Report for the subject with randomization number 3001

matches (b) (4) ANC results for Screen ID 3002 at PRA. We note that the protocol called for use of the randomization number only, once subjects were enrolled into the study.

This inspection audited only ANC records at (b) (4) not clinical portions of the study at PRA in Lenexa. At the conclusion of the inspection, Ms. White did not issue Form FDA 483 at (b) (4).

4. Conclusion:

After reviewing the inspectional findings at (b) (4) I conclude that ANC data for subjects at PRA in Lenexa for study LA-EP06-104 were verified. However, a typographical error was identified in the clinical study report submitted to FDA (**ATTACHMENT 1**). There were also errors in transcribing randomization numbers for (b) (4) ANC results (**ATTACHMENT 4**). I suggest that the Division of Hematology Products should invite the study sponsor to confirm records, in order to match subject identities to treatments, clinical observations, and ANC data.

VAI -

(b) (4)

cc:

OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/CDER-OSISBEQ@
fda.hhs.gov

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Li

ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: XFL 06/27/2019; 07/8/2019; 07/9/2019; 07/22/2019;
7/25/2019

Edit: MFS 06/28/2019; 07/09/2019; JAK 07/17/2019; 07/25/2019;
7/26/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/

(b) (4)

OSIS File #: (b) (4) (BLA 761045)

FACTS:

(b) (4)

ATTACHMENT: 1

30 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XINGFANG LI
07/26/2019 12:54:15 PM

JOHN A KADAVIL
07/26/2019 01:11:11 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 15, 2019

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Carole Broadnax, RPh, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (non-proprietary name): TRADENAME (pegfilgrastim-xxxx)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761045

Applicant: Sandoz, Inc.

¹ LA-EP2006 has been developed as a biosimilar to US-licensed pegfilgrastim. At the time of this review, the proprietary name has not yet been determined; therefore, we use TRADENAME as a placeholder until such time as it has been determined. The non-proprietary name has not been determined; therefore, we use pegfilgrastim-xxxx as a placeholder until such time as it has been determined.

1 INTRODUCTION

On February 27, 2019, Sandoz, Inc. submitted for the Agency's review a Class 2 Complete Response to the Agency's Complete Response (CR) letter issued on June 24, 2016 for their original Biologics License Application (BLA) 761045 for LA-EP2006, TRADENAME (pegfilgrastim-xxxx), a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim). On May 28, 2019, the Division of Medication Error and Prevention Analysis (DMEPA) found the proposed proprietary name Ziextenzo unacceptable. On June 21, 2019, the Applicant submitted a Request for Reconsideration of Proprietary Name. The Proprietary Name is under reconsideration by the Agency at the time of this review.

The proposed indication for LA-EP2006, TRADENAME (pegfilgrastim-xxxx) is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on May 24, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (pegfilgrastim-xxxx) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft TRADENAME (pegfilgrastim-xxxx) injection PPI and IFU received on February 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 23, 2019 and July 2, 2019.
- Draft TRADENAME (pegfilgrastim-xxxx) injection Prescribing Information (PI) received on February 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on July 2, 2019.
- Approved US-licensed Neulasta (pegfilgrastim) injection labeling dated April 16, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- evaluated the PPI and IFU per the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved labeling for US-licensed Neulasta where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON R MILLS
07/15/2019 05:28:52 PM

SUSANNAH O'DONNELL on behalf of CAROLE C BROADNAX
07/16/2019 07:22:48 AM

LASHAWN M GRIFFITHS
07/16/2019 07:37:30 AM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 9, 2019

TO: Patricia Keegan, MD
Division Director
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

and

Ann T. Farrell, MD
Division Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDBE, OSIS

SUBJECT: Routine inspection of Celerion Arizona, Tempe, AZ
supporting clinical studies RXDX-101-15 (NDA 212725
and NDA 212726) and LA-EP06-104 (BLA 761045)

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of studies RXDX-101-15 (NDA 212725 and NDA 212726) and LA-EP06-104 (BLA 761045) conducted at Celerion Arizona, Tempe, AZ.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. However, the blinding codes for study LA-EP06-104 (BLA 761045) were not in Celerion's possession during the interval between study completion and the inspection. The final classification for Celerion Arizona, Tempe, AZ, USA is Voluntary Action Indicated (VAI).

1.1. Recommendation

After reviewing the inspectional findings, the blinding codes for LA-EP06-104 (BLA 761045) were not in Celerion's possession after study completion. The data from study LA-EP06-104 are not reliable to support a regulatory decision, because FDA cannot confirm accurate dosing. However, the inspectional findings were isolated in nature and do not impact the reliability of data from study RXDX-101-15. Therefore, data from study RXDX-101-15 and other studies of similar design (open-label) are reliable to support a regulatory decision.

I conclude that data from the audited study RXDX-101-15 (NDA 212725 & NDA 212726) are reliable to support a regulatory decision. However, I recommend excluding data generated at Celerion for study LA-EP06-104 (BLA 761045).

2 Inspected Studies:

NDA 212725 and NDA 212726

Study Number: RXDX-101-15

Study Title: "A 2-Part, Open-Label, Randomized, 2-Period, Single-Dose Study to Assess the Relative Bioavailability of 2 Entrectinib Formulations Under Fasting Conditions and the Effect of Food on the Entrectinib F06 Formulation in Healthy Adult Male Subjects"

Dates of conduct: 02/16/2018 - 06/6/2018

BLA 761045

Study Number: LA-EP06-104

Study Title: "A randomized, double blind, crossover, three-way blinded study to compare the pharmacokinetics, pharmacodynamics, and safety of a single 6 mg subcutaneous administration of the proposed biosimilar product LA EP-2006, Neulasta US and Neulasta EU in healthy subjects"

Dates of conduct: 04/14/2017- 08/01/2018

Clinical site: Celerion Arizona
2420 West Baseline Road
Tempe, AZ
FEI#: 3009853739

ORA investigator Michelle Hines (LOS-DO) inspected Celerion Arizona, 2420 West Baseline Road Tempe, AZ from May 28 to June 5, 2019.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

Study LA-EP06-104 was designed as a double blind study. During the inspection, Ms. Hines requested access to the blinding codes to verify subject treatments. However, there were no blinding codes in Celerion's possession at that time (**Attachment 1**). It is important to note that all blinding codes were paper-based, as described in **Attachment 2**. The study did not utilize any type of Interactive Response Technology (e.g. interactive voice or web response systems) that would have maintained blinding codes and associated audit trails. Therefore, no such system was available to ORA for verifying subject treatments.

At the conclusion of the inspection, investigator Hines did not observe objectionable conditions and did not issue Form FDA 483 to the clinical site. However, because the blinding codes for study LA-EP06-104 (BLA 761045) were not in Celerion's possession from the end of the study through the inspection, investigator Hines could not verify accuracy of dosing with the blinded products.

4. Conclusion:

After reviewing the inspectional findings at Celerion Arizona, I conclude the following:

- The data from study RXDX-101-15 are reliable. I recommend that data from study RXDX-101-15 should be accepted for further agency review.
- The data for LA-EP06-104 are NOT reliable, because FDA cannot verify accuracy of dosing with the intended products in the absence of intact blinding codes. Based on the inspectional findings, I recommend that data from study LA-EP06-104 not be accepted for further agency review. The review division may request the sponsor to submit documentation to mitigate the uncertainty of accurate dosing.

In addition, I recommend that data from other blinded studies conducted at Celerion Arizona since the previous inspection (August 2015) should not be accepted for agency

review without an inspection to authenticate the dosing records.

Final Classification:

VAI - Celerion Arizona,
Tempe, AZ
USA
FEI#: 3009853739

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/CDER-OSISBEQ@
fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Li

ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: XFL 06/24/2019; 7/5/2019; 7/9/2019
Edit: MFS 06/25/2019 and 07/05/2019; JAK 07/05/2019 and
07/08/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/Celerion, Tempe,
AZ, USA

OSIS File #: 8372 (NDA 212725)
8373 (NDA 212726)
7016 (BLA 761045)

FACTS: 11908319

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XINGFANG LI
07/09/2019 02:54:29 PM

MICHAEL F SKELLY
07/09/2019 02:57:20 PM

JOHN A KADAVIL
07/09/2019 03:02:21 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 06/12/2019
To: Administrative File, **STN 761045-1-RESUB-49**
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for **LA-EP2006**
US License: 2003
Applicant: Sandoz, Inc.
Mfg Facility: Drug Substance:
Sandoz GmbH, Biochemiestrasse 10, Kundl, Austria FEI 3002806523
Lek Pharmaceuticals d.d., Kolodvorska 27, Mengeš, Slovenia FEI 3002807470
Drug Product:

(b) (4)

Product: LA-EP2006
Dosage: Injectable sterile, clear and colorless solution for subcutaneous administration. Single use pre-filled syringe containing 6 mg/0.6 mL (10 mg/mL).
Indication: Therapeutic to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia..
Due Date: 08/27/2019

RECOMMENDATION: This application is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes the manufacture of LA-EP2006 Drug Substance and Drug Product at the Sandoz GmbH, Lek Pharmaceuticals d.d., and (b) (4). The starting material

(b) (4)

(b) (4)
The drug substance (b) (4) is manufactured at Lek Pharmaceuticals d.d. (Mengeš, Slovenia), a subsidiary of Sandoz. LA-EP2006 Drug Product is manufactured at (b) (4) in the final

BLA 761045/0. LA-EP2006 DS and DP Manufacture

primary packaging (syringes). Sandoz GmbH releases the LA-EP2006 6 mg/0.6 mL solution for injection. In addition to the sites mentioned above in the manufacturer of LA-EP2006 6 mg/0.6 mL, Novartis Pharma AG, Lek Pharmaceuticals d.d. Ljubljana, and (b) (4) perform testing of the DS and DP. A Pre-license inspection was conducted on 03/08 – 14/2016 at Lek Pharmaceutical d.d. No FDA Form 483 was issued, and a final recommendation of acceptable (NAI) has been made. A For Cause and Pre-license inspection was conducted on (b) (4) at (b) (4). A six-item FDA Form 483 was issued, and a final recommendation of acceptable (VAI) has been made. All other related DS and DP facilities have an acceptable compliance status.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S Drug Substance [Substance – Manufacturer]

3.2.S.2. Manufacture

3.2.S.2.1 DS Manufacturers.

The site proposed for LA-EP2006 Drug Substance manufacture, cell banking operations, and testing is presented below in Table 1.

Table 1. Proposed Sites for LA-EP2006 DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Sandoz GmbH	Biochemiestrasse 10 AT-6250 Kundl, Austria	3002806523	The EP2006 (b) (4) is manufactured and tested (according to current Good Manufacturing Practices - cGMP). Preparation of the WCB, and storage of the MCB and WCB.
Lek Pharmaceuticals d.d. (a Sandoz company)	Kolodvorska 27 SI-1234 Mengeš, Slovenia	3002807470	The LA-EP2006 drug substance (pegylated EP-2006) is manufactured by pegylation of the EP2006 (b) (4) tested and released (according to current Good Manufacturing Practices - cGMP).
(b) (4)			DS testing.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DS testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DS testing.

Reviewer Comment 1: The facilities for manufacture of LA-EP2006 DS are adequately described.

• Prior Inspection History for DS Manufacturing and Testing Sites

BLA 761045/0. LA-EP2006 DS and DP Manufacture

Sandoz GmbH (FEI 3002806523), EP2006 (b) (4) (unpegylated) manufacture, IPC and release testing. A comprehensive surveillance inspection conducted on 04/30/2015 for profiles BTP, CHG, CSN, CSS, CTX, POW, SPW, SVS, TCM, TTR, and CBI included evaluation of the Quality Systems, Facilities and Equipment, Production, and Laboratory Control Systems supporting production of drug substances including biologically derived drug substances, sterile powders for injection, and solid oral dosage forms. This inspection was VAI and found acceptable. Additionally, a comprehensive surveillance and Pre-approval Inspection for EP2006, BLA 125553, and BLA 125546 (Bexsero vaccine) was conducted on 09/16/2014 that covered the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Systems for Profiles CBI, CSS, CTX, SPW, SVS, and VBP. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470), LA-EP2006 drug substance manufacture by pegylation of the EP2006 (b) (4) IPC and release testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

Novartis Pharma AG (FEI 3002807772), Drug Substance release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products: (b) (4) Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460), Drug Substance release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable. (b) (4)

This inspection was VAI and found acceptable.

- **Current Prior Approval Inspection Decisions**

BLA 761045/0. LA-EP2006 DS and DP Manufacture

Sandoz GmbH (FEI 3010479596). DIA, DMA, and OBP waived a PLI for this facility because a PLI for EP2006 was conducted on 09/16/2014, and this justification was documented in the waiver memo . A District file review was requested and the site was found acceptable based on file review.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470). DIA, DMA, and OBP conducted a joint PLI for LA-EP2006 drug substance at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

(b) (4)

Novartis Pharma AG (FEI 3002807772) was approved based on the facility CTL profile.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

***Reviewer Comment 2:** A recommendation regarding the compliance status for the DS production and testing facilities associated with the manufacture of LA-EP2006 is acceptable.*

3.2.S.2.2 Overview of LA-EP2006 DS Manufacturing Operations Conducted at Sandoz GmbH and Lek Pharmaceuticals d.d.

(b) (4)

***Reviewer Comment 3:** The overview of EP2006 (b) (4) manufacturing operations conducted at Sandoz GmbH and LA-EP2006 DS manufacturing operations conducted at Lek Pharmaceuticals d.d. are adequately described. The EP2006 DS manufacturing operations were previously verified during the September 2014 inspection, and these operations are identical to those of the EP2006 (b) (4). The LA-EP2006 DS manufacturing operation was verified during the March 2016 inspection.*

3.2.A. Appendices

BLA 761045/0. LA-EP2006 DS and DP Manufacture

3.2.A.1 Facilities and Equipment [Manufacturer – substance – Dosage Form – Product]

(b) (4)



BLA 761045/0. LA-EP2006 DS and DP Manufacture

(b) (4)

DRUG PRODUCT FACILITIES

3.2.P Drug Product [Substance – Manufacturer]

3.2.P.2. Manufacture

3.2.P.2.1 DP Manufacturers.

The site proposed for LA-EP2006 Drug Product manufacture, cell banking operations, and testing is presented below in Table 12.

TABLE 12. Proposed Sites for LA-EP2006 DP Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
(b) (4)			LA-EP2006 6 mg/0.6 mL DP solution for injection is manufactured, tested, and packaged.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DP Bioactivity testing.
Sandoz GmbH	Biochemiestraße 10 6336 Langkampfen Austria	3004828473	DP stability testing.
Lek Pharmaceuticals d.d.	Kolodvorska Cesta 27 Mengeš, 1234 Slovenia	3002807470	DP testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DP testing.

Reviewer Comment 23: *The facilities for manufacture of LA-EP2006 DP are adequately described.*

BLA 761045/0. LA-EP2006 DS and DP Manufacture

- **Prior Inspection History for DS Manufacturing and Testing Sites**

(b) (4)

Novartis Pharma AG (FEI 3002807772), Drug Product release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products: (b) (4) (b) (4) Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing. A comprehensive surveillance inspection conducted on 03/18/2014 for profiles CRU, CXA, and SVS included evaluation of the Quality, Production, Laboratory Control, Materials and Facility and Equipment Systems. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance Inspection was conducted on 03/16/2012 that covered the Quality, Production, Facilities & Equipment, and Laboratory Control Systems for Profiles SVS, CXA, CBI, CSN and TAM. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470), Drug Product release and stability testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d., Ljubljana, Slovenia (FEI 3002807460), Drug Product release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable. (b) (4)

(b) (4) This inspection was VAI and found acceptable.

BLA 761045/0. LA-EP2006 DS and DP Manufacture

- **Current Prior Approval Inspection Decisions**



Novartis Pharma AG (FEI 3002807772) was approved based on the facility profile and Laboratory Control Systems coverage.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing was approved based on the facility profile and Laboratory Control Systems coverage.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470). DAI, DMA, and OBP conducted a joint pre-approval inspection for LA-EP2006 drug substance (pegylated EP2006) that included Laboratory Control Systems at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

Reviewer Comment 24: *the compliance statuses for the DP production and testing facilities associated with the manufacture of LA-EP2006 are acceptable.*



BLA 761045/0. LA-EP2006 DS and DP Manufacture

(b) (4)

CONCLUSION

Adequate descriptions were provided for the Sandoz GmbH (FEI 3002806523) and Lek Pharmaceuticals d.d. (FEI 3002807470) LA-EP2006 Drug Substance facilities, and (b) (4) LA-EP2006 Drug Product facility proposed for DS and DP manufacture. The proposed DS and DP manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

Michael Shanks, Biologist, CDER/OPQ/OPF/DIA I 05/20/2016

Zhihao Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA I 05/20/2016

BLA 761045-1-RESUB-49

CONCLUSION

No changes from the original submission from a Facilities Perspective and adequate descriptions were provided for the Sandoz GmbH (FEI 3002806523) and Lek Pharmaceuticals d.d. (FEI 3002807470) LA-EP2006 Drug Substance facilities, and (b) (4) LA-EP2006 Drug Product facility proposed for DS and DP manufacture. The proposed DS and DP manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

Michael R.
Shanks -S

Digitally signed by Michael R. Shanks -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200140831
7, cn=Michael R. Shanks -S
Date: 2019.06.12 10:11:19 -04'00'

Michael Shanks
Biologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Zhihao Qiu -S,
0.9.2342.19200300.100.1.1=2000438274
Date: 2019.06.12 10:18:20 -04'00'

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	BLLA 761045
Applicant	Sandoz
Proprietary Name (nonproprietary name)	Proposed Proprietary Name: ZIEXTENZO (pegfilgrastim-xxxx)
Receipt Date	02/27/19
PDUFA Goal Date (Internal Goal Date)	08/27/19
Review Classification	Response to CR; 6 month clock
Proposed Indication (or current indication if unchanged)	ZIEXTENZO is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Dosing Regimen	
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

In this review, I summarize the DHP labeling recommendations and edits in the LA-EP2006 (pegfilgrastim-xxxx; ZIEXTENZO) labeling. ZIEXTENZO (pegfilgrastim-xxxx) is a proposed biosimilar product to Neulasta (pegfilgrastim). This BLA previously received a Complete Response on 06/04/16 for product quality and clinical pharmacology issues. Sandoz has submitted their response to CR.

These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of ZIEXTENZO.

I compared the proposed labeling to the April 2019 version of the approved Neulasta labeling. I highlighted/commented on areas where there were differences and made recommendations as how to approach these differences. The edits suggested are to align with the currently approved version of the Neulasta labeling.

The following pages contain a summary of the labeling recommendations followed by the working version of the ZIEXTENZO labeling with comments by me identified by “KV##” and sequentially numbered. Given that the scientific review of the labeling is ongoing, the labeling recommendations in this review should be considered preliminary and may not represent DHP’s final recommendations for the ZIEXTENZO labeling.

Summary of Labeling Recommendations:

Highlights

Dosage Forms and Strengths:

- Removed “(b) (4)” to provide a concise summary of the USPI in Highlights. These details are also not consistent with Section 3 of the FPI.

Full Prescribing Information

Dosage and Administration:

- Section 2.2: Recommend removal of text “(the solution is clear and colorless to slightly yellowish)” as inclusion of the description within parentheses may confuse readers into believing they should not administer a solution that is clear and colorless to slightly yellowish. The usual appearance is described in Section 3.

Adverse Reactions:

- Section 6.3: Added “alveolar hemorrhage” to the list of events in the Postmarketing Experience to be consistent with recently approved Neulasta labeling (April 2019).

Use in Specific Populations:

- Section 8.1 Pregnancy: Revised formatting of “(see Data)” to italics to be consistent with PLLR guidance and Neulasta USPI.

Description:

- Recommend removal of period in “E coli” to be consistent with Neulasta USPI. It is grammatically correct, but labeling should be consistent with innovator product.
- Corrected capitalization of “water for injection, USP” to “Water for Injection, USP” to be consistent with USP and the Neulasta USPI.

Text after Patient Counseling (Section 17):

- Requested that Applicant add the street address of the manufacturer. Per 21 CFR 201.1 and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling and should be located after the Patient Counseling Information section, at the end of the PI. If the product has FDA-approved patient labeling that is not a separate document from the PI, the manufacturer information should be located at the end of labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document, or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling. The street address may be omitted if it is shown in a current city directory or telephone directory.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIRGINIA E KWITKOWSKI
05/29/2019 11:13:59 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/12/2019

TO: Division of Hematology Products
Office of New Drugs

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761045

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

PRA Health Sciences, Groningen: The Office of Regulatory Affairs (ORA) inspected the site in April 2017, which falls within the surveillance interval. The inspection was conducted under the following submission: BLA 761075.

PRA Health Sciences, Salt Lake City: The Office of Regulatory Affairs (ORA) inspected the site in November 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA 212038.

Celerion, Lincoln: The Office of Regulatory Affairs (ORA) inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submission:

(b) (4)

(b) (4)

Therefore, based on the outcome of the previous inspections and the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	PRA Health Sciences	Clinical Chemistry Laboratory, Van Swietenlaan 6, 9728 NZ Groningen, The Netherlands
Clinical	PRA Health Sciences	700 East 3838 South, Suite 200, Salt Lake City, UT

Facility Type	Facility Name	Facility Address
Clinical	Celerion	621 Rose Street, Lincoln, NE
Analytical	(b) (4)	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLA M FENTY-STEWART
04/12/2019 06:09:15 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: 6/28/2016

To: Rachael McMullen, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Office of Prescription Drug Promotion

Through: Katie Davis, Team Leader
Office of Prescription Drug Promotion

Subject: Comments on draft labeling (Package Insert) for LA-EP2006
(pegfilgrastim)/BLA 761045

This memo is in response to your labeling consult request on October 20, 2015. DHP issued a Complete Response (CR) letter on June 24, 2016. Therefore, OPDP defers comment on the Applicant's labeling at this time. A comprehensive review of the proposed patient labeling will not be performed until after the Applicant submits an otherwise adequate application. Please send us a new consult request at such time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES S DVORSKY
06/28/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 23, 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761045
Product Name and Strength:	Ziextenzo (LA-EP2006)* Injection 6 mg/0.6 mL
Product Type:	Single Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sandoz
Submission Date:	August 27, 2015
OSE RCM #:	2015-2000
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Ziextenzo (LA-EP2006)* injection (BLA 761045) for areas of vulnerability that could lead to medication errors. The Division of Hematology Products (DHP) requested this review to inform their evaluation of the 351(k) submission for Ziextenzo. The reference product, US-licensed Neulasta (BLA 125031), was approved in January 2002.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)#	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

#We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Ziextenzo (LA-EP2006)* injection, BLA 761045. We note that Ziextenzo has the same route of administration, strength, and storage requirements as the reference product, US-licensed Neulasta (BLA 125031). At the time when the Ziextenzo 351(k) BLA was submitted (August 27, 2015), there was no information regarding pediatric dosing in US-licensed Neulasta labeling. Since then, weight based dosing which would allow dosing of patients less than 45 kg, including pediatric patients, for the indications of decreasing the incidence of infection in patients with cancer receiving myelosuppressive chemotherapy and hematopoietic subsyndrome of acute radiation syndrome (ARS) were added to the labeling of US-licensed Neulasta. It is noted that if Sandoz can demonstrate that LA-EP2006 is biosimilar to

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

US-licensed Neulasta, they can be licensed for the indication of decreasing the incidence of infection in both pediatric (because of weight-based dosing information in the reference product) and adult patients with cancer receiving myelosuppressive chemotherapy but cannot be licensed for ARS as the sponsor of US-licensed Neulasta has unexpired orphan-drug exclusivity for this indication.

Per discussion with the Division of Pediatric and Maternal Health (DPMH), Ziextenzo is subject to the Pediatric Research Equity Act (PREA) as a biosimilar product, and thus a pediatric assessment is required unless waived or deferred (see section 505B(m) of the FD&C Act). A pediatric assessment must include data gathered using an age-appropriate formulation or formulations that are adequate to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the biological product is safe and effective (see section 505B(a)(2)(A) of the FD&C Act). The pediatric formulation or formulations should be capable of being accurately administered in all relevant pediatric populations.

Ziextenzo is supplied as a single-use prefilled syringe (PFS) with an UltraSafe Passive™ needle guard. The Ziextenzo PFS does not have graduation marks. US-licensed Neulasta is supplied as a single-use PFS with a manual needle guard and as a PFS for use with a delivery device, the OnPro kit. Similar to the Ziextenzo PFS, the US-licensed Neulasta PFS also does not have graduation marks, but dosing for the reference product, US-licensed Neulasta, includes pediatric doses of less than 6 mg (0.6 mL). Because the Ziextenzo's PFS, like the US-licensed Neulasta's PFS, does not have graduation marks, doses less than 6 mg (0.6 mL) cannot be accurately measured or directly administered without manipulation of the PFS content or dose approximation, both of which can lead to medication errors, as has been evidenced by postmarket reports of "lack of calibration" on the PFS as a factor that contributed to dosing errors with off label use of US-licensed Neulasta.¹

Prefilled syringes are generally designed for direct patient administration. Syringes are also among the most commonly used devices to deliver drugs, and, as a general matter, they tend to have calibrated graduation marks that allow for accurate measurement of variable amounts of fluid. Collectively, these factors will likely predispose some practitioners who are ordering, dispensing or administering a prefilled syringe not consult the label for this administration

¹ Ayres, Ebony. Label and Labeling Review for Neulasta BLA 125031/S-180. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 23. RCM No.: 2015-1012.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

aspect. Thus, there is some likelihood that practitioners will mistakenly assume that the PFS can accurately measure a variable range of doses to be directly administered to a patient.

However, labeling statements in the US-licensed Neulasta labeling clearly advise that the PFS is not designed for direct administration of the drug for doses less than 0.6mL (6 mg). Similar statements appear in the Zarxio (filgrastim-sndz) labeling approved in March 2015. These statements should reduce the risk of error in circumstances where the label is read and attended to by providers.

Thus, we determined that the issue of the PFS not being designed for direct administration of doses less than 6 mg (0.6 mL) in the current proposed Ziextenzo presentation could be addressed through modifications to Ziextenzo's proposed labeling. Specifically, we recommend that the design limitations of the PFS be conveyed as important information about the device to consider under the Dosage and Administration, Description, and How Supplied/Storage and Handling sections of the PI and within the IFU, consistent with the labeling of Zarxio and US-licensed Neulasta.

Ziextenzo, however, is subject to PREA, which requires the development of an appropriate pediatric presentation or presentations for all relevant pediatric subpopulations. While the labeling statements discussed above and in section 4 of this review mitigate the risk of medication errors in patients weighing less than 45 kg, we note that the Ziextenzo PFS is not designed to measure a variable amount of liquid that corresponds to the labeled doses.

These refinements could be made prior to approval. Alternatively, if FDA defers the pediatric assessment associated with this BLA, the development of an appropriate pediatric presentation would be done as a Post-Marketing Requirement (PMR). If these refinements are made as a PMR, the PMR should outline the need for Sandoz to develop a presentation that can be used to directly administer doses less than 6 mg (0.6 mL) and should also convey that the proposed presentations may need Human Factors studies to demonstrate that users can accurately measure the doses.

If the sponsor continues to seek approval of the current proposed presentation, the PI for Ziextenzo should be revised to include the same weight-based dosing information for patients with cancer receiving myelosuppressive chemotherapy, i.e., section 2 Dosage and Administration of the PI should be revised to include a weight-based dosing table mirroring Table 1 in the US-licensed Neulasta PI.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

The Ziextenzo IFU follows similar steps and injection technique as the reference product, US-licensed Neulasta. However, we recommend areas within the Ziextenzo IFU that differ from US-licensed Neulasta IFU be revised to be harmonized with the US-licensed Neulasta IFU. For example, US-licensed Neulasta can be administered at either a 45° or 90° angle. However, in the Ziextenzo IFU, the graphic depicting the injection technique shows an approximately 45° injection angle, and the text accompanying the graphic does not state the injection angle. Revision of this step may help to decrease the risk of confusion regarding the injection technique and will harmonize this step with the US-licensed Neulasta IFU. We also note that the Ziextenzo IFU does not list or depict the buttocks as an injection site. This aspect also differs from the reference product, US-licensed Neulasta. We recommend that this discrepancy is clarified and that the injection sites are revised, if appropriate to include the buttocks injection site. We defer to the Clinical team and Patient Labeling team to provide additional recommendations for the Ziextenzo IFU.

The carton labeling and container labeling can be improved to increase the visibility and clarity of key prescribing information, and to increase the prominence of the storage information. Our post-marketing experience also demonstrates that the net quantity (i.e., 1 prefilled syringe) may be misinterpreted as product strength (i.e., 6 mg/0.6mL) and thus, dosing errors may occur. Accordingly, the prominence of the net quantity should be reduced relative to the strength statement to decrease the risk of confusion, as recommended in the draft guidance for industry: Safety Considerations for Container Labels and Carton labeling Design to Minimize Medication Error.² Additionally, the labeling should be updated to revise the trade name from (b) (4) to Ziextenzo. We also note the presence of a removable label on the Ziextenzo PFS, which may temporarily adhere to the syringe body and interfere with syringe visibility. In response to a March 15, 2016 Information Request from the Agency, the Sponsor stated that the purpose of the removable label is for documentation purposes and medication error prevention. We do not recommend revisions to the removable label at this time; however, we will monitor postmarketing reports for instances of medication errors or difficulties with the removable label.

We searched the FAERS database to identify medication errors with the reference product US-licensed Neulasta that may be relevant to this review. We identified fifty-six medication error cases including inappropriate schedule of administration, incorrect route of administration, and

² Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

improper storage (see Appendix E for a detailed description of the cases). We evaluated the Ziextenzo labels and labeling in light of the US-licensed Neulasta medication errors to ensure that information regarding the route and frequency of administration is clear and prominent, and we did not identify any needed changes. The reports of incorrect storage of US-licensed Neulasta reported US-licensed Neulasta being stored outside of refrigeration. Based on this finding, we recommend that the proposed carton labeling for Ziextenzo be revised to increase the prominence of the storage information to help mitigate the risk for incorrect storage errors.

4 CONCLUSION & RECOMMENDATIONS

Our review identified risk for medication errors in patients who weigh less than 45 kg, e.g., pediatric patients, because the U.S. Neulasta PFS and proposed Ziextenzo PFS are not designed for the direct administration of doses less than 0.6 mL (6 mg) due to lack of graduation marks. We provide specific recommendations on the proposed Ziextenzo labeling below, consistent with labeling statements for Neulasta, to mitigate this risk if the sponsor continues to seek approval of the current proposed presentation.

Because Ziextenzo is subject to PREA, however, an appropriate pediatric presentation will have to be developed. The sponsor could do this prior to approval or, if FDA defers the pediatric assessment associated with this BLA, development of an appropriate pediatric presentation will be required as a PMR.

Additionally, we identified other aspects of the labels and labeling that should be revised to add important information regarding the administration of pediatric doses if the sponsor continues to seek approval of the current proposed presentation, harmonize with the labeling for the reference product where appropriate, and to mitigate the risk of medication errors. We provide recommendations below, and we advise they are implemented prior to approval of BLA 761045.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Pediatric Presentation

- a. Ziextenzo is subject to the Pediatric Research Equity Act (PREA) as a biosimilar product. Thus, the application must include a pediatric assessment, which includes development of an appropriate pediatric presentation. The proposed presentation(s) may need Human Factors studies to demonstrate that users can accurately measure the doses. The proposed pediatric presentation(s) can be developed prior to approval, or the Sponsor can request a deferral of the pediatric assessment pending development of an appropriate pediatric

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

presentation. If the Sponsor chooses the latter approach, the development of an appropriate pediatric presentation will be required as a post marketing requirement (PMR).

B. Prescribing Information

- a. Update the trade name on the labeling from (b) (4) to Ziextenzo.
- b. *If the sponsor continues to seek approval of the current proposed presentation:*
Section 2 Dosage and Administration
 - i. 2.2 Administration
 1. Include the following statement in this section to inform users that Ziextenzo prefilled syringes cannot be used for the direct administration of doses less than 6 mg (0.6 mL):
 - a. The Ziextenzo prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks which are necessary to accurately measure doses of Ziextenzo less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors.
 2. We recommend including a dosing table for patients weighing less than 45 kg (see Table 1 under Section 2 of the PI for Neulasta)
- c. *If the sponsor continues to seek approval of the current proposed presentation:*
Section 11 Description
 - i. Following the sentence, “(b) (4) is supplied in 0.6 mL prefilled syringes for subcutaneous injection”, include the following statement to inform users that Ziextenzo prefilled syringes cannot be used for the direct administration of doses less than 6 mg (0.6 mL):
 1. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).
- d. *If the sponsor continues to seek approval of the current proposed presentation:*
Section 16 How Supplied/Storage and Handling
 - i. Include the following statement to inform users that Ziextenzo prefilled syringes cannot be used for the direct administration of doses less than 6 mg (0.6 mL):

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

1. Ziextenzo prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

4.2 RECOMMENDATIONS FOR SANDOZ

We recommend the following be implemented prior to approval of this BLA 761045:

A. Carton labeling (outer)

1. Update the trade name on the labeling from (b) (4) to Ziextenzo.
2. Consider the use of boldface font to increase the prominence of “Refrigerate” on the principal display panel (PDP) to help mitigate the risk of improper storage errors.
3. Decrease the prominence of the net quantity “1” because this information appears with equal prominence to the product strength (i.e., 6 mg/0.6mL) and may increase the risk of numerical confusion.³

B. Carton labeling (inner)

1. Refer to recommendation A.1. and revise accordingly.

C. Container label (syringe label)

1. Refer to recommendation A.1. and revise accordingly.

D. Instructions for Use

1. Refer to recommendation A.1. and revise accordingly.
2. *If the sponsor continues to seek approval of the current proposed presentation:* In the first section of the IFU, include the following statement to indicate to users that Ziextenzo cannot be used to directly administer doses less than 6 mg (0.6 mL):
 - i. You should not inject a dose of Ziextenzo less than 0.6 mL (6 mg) from a Ziextenzo prefilled syringe. A dose less than 0.6 mL cannot be accurately measured using the Ziextenzo prefilled syringe.
3. Consider removing the label “(b) (4)” from Figure A as this technical term may not be understood by patients and caretakers. Additionally, this term is not referenced in the remainder of the IFU.

³ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

4. In Step 8, replace the term “transparent” with “clear” to mitigate the risk of confusion as patients and caretakers may not understand the term “transparent”.
5. In Step 10, revise the sentence “(b) (4)” to “Let the skin dry.” We recommend this revision to increase the clarity of this statement.
6. In Step 14, Figure J shows the Ziextenzo injection being given at an approximately 45° angle. The text in Step 14 does not mention at which angle the injection should be given. Therefore, revise the text in Step 14 to include the injection angle that should be used to administer Ziextenzo.
7. We note the IFU does not list the buttocks as an injection. The upper outer area of the buttocks is listed as an injection site for the reference product, US-licensed Neulasta. Therefore, please clarify and provide reasoning for the discrepancy between the Ziextenzo IFU and the US-licensed Neulasta IFU.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ziextenzo that Sandoz submitted on August 27, 2015, and the reference product.

Table 2. Relevant Product Information for Ziextenzo and the Listed Drug		
Product Name	Ziextenzo	Neulasta
Initial Approval Date	N/A	January 31, 2002
Active Ingredient	LA-EP2006*	Pegylated-GCSF
Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	<ul style="list-style-type: none"> - To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia - Improve survival in adult victims and pediatric victims with body weight \geq 45 kg who are at risk of developing life-threatening infections secondary to neutropenia resulting from acute exposure to radiation levels > 2 Gy.
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection, solution	Injection, solution
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Dose and Frequency	<p>Give 6 mg subcutaneously once per chemotherapy cycle.</p> <p><i>Additional dosing proposed by DHP:</i> For pediatric patients weighing less than 45 kg, use weight</p>	<p><i>Cancer patients receiving myelosuppressive chemotherapy</i></p> <ul style="list-style-type: none"> - 6 mg administered subcutaneously once per chemotherapy cycle; for pediatric patients weighing less than 45 kg, use weight

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

	based dosing (100 mcg/kg)	<p>based dosing (100 mcg/kg)</p> <p><i>Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome</i></p> <ul style="list-style-type: none"> - 6 mg subcutaneously for adult victims and for pediatric victims with body weight \geq 45 kg for two doses given two weeks apart; for pediatric patients weighing less than 45 kg, use weight based dosing (100 mcg/kg)
How Supplied	Single-dose, preservative-free, prefilled syringe with an UltraSafe Passive™ Needle Guard, containing 6 mg/0.6 mL of LA-EP2006*.	<ul style="list-style-type: none"> - 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only - OnPro kit: 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta
Storage	<p>Store in the refrigerator at 36°F to 46°F (2°C to 8°C) in the original pack to protect from light. Do not shake. Do not freeze. Prior to injection, Ziextenzo may be allowed to reach room temperature for a</p> <p>(b) (4)</p>	<p>Store refrigerated between 36° to 46°F (2° to 8°C) in the carton to protect from light.</p>

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 21, 2015, we searched the L:drive and AIMS using the term, Ziextenzo, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**E.1 Methods**

We searched the FDA Adverse Event Reporting System (FAERS) on November 30, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.⁴

Table 3: FAERS Search Strategy	
Date Range	FDA Received Date To: 20151101
Product	Neulasta [active ingredient] pegfilgrastim [product name]
Event (MedDRA Terms)	Contraindicated drug administered [PT] Drug administered to patient of inappropriate age [PT] Inadequate aseptic technique in use of product [PT] Medication errors [HLGT] Overdose [PT] Prescribed overdose [PT] Prescribed underdose [PT] Product adhesion issue [PT] Product compounding quality issue [PT] Product formulation issue [PT] Product label issues[HLT] Product packaging issues [HLT] Product use issue [PT] Underdose [PT]
Country	USA

Our search identified 132 cases, of which 56 described medication errors relevant for this review. Some cases described more than one type of medication error.

Inappropriate schedule of administration (n = 22)

- Twenty-two cases reported inappropriate schedule of administration of US-licensed Neulasta (FAERS Case No. 10777949, 11627136, 5766272, 5770507, 6597246, 6597285,

⁴ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

6597317, 6944160, 6944208, 6987263, 7083087, 7330371, 7885017, 7885071, 8776703, 9871756, 9871776, 8702433, 8093450, 9256070, 9256189, 9256242).

- Eleven cases described patients who accidentally received more than one dose of Neulasta during a given cycle of chemotherapy.
- Two cases described reports of two separate patients receiving doses of US-licensed Neulasta less than 24 hours after receiving chemotherapy.
- Regarding contributing factors, one case listed “something wrong with the orders” as a contributing factor. Another case listed a change in scheduling due to the holiday as a contributing factor.
- Regarding patient outcomes, two cases reported that patients experienced bone pain in response to the errors. One case reported that the inappropriate schedule of administration of US-licensed Neulasta caused an increase in tumor size. One case reported that a patient did not experience adverse events as a result of the medication error. One case reported that the patient felt ill after receiving US-licensed Neulasta earlier than scheduled. The remaining cases did not provide patient outcomes or contributing factors.

A review of Section 2 Dosage and Administration of the Prescribing Information of the reference product indicates that US-licensed Neulasta should be administered once per chemotherapy cycle and should not be administered between 14 days before and 24 hours after administration of chemotherapy. The information appears to be clearly listed. This dosing information in the Prescribing Information for Ziextenzo is identical to the reference product; as a result, we do not believe labeling revisions are not necessary at this time.

Incorrect route of administration (n = 11)

- Eleven cases (FAERS Case No. 10136263, 10777995, 11517529, 11617255, 7331621, 8393053, 8435610, 9256079, 9256118, 9256194, 9256250) described the administration of US-licensed Neulasta via an incorrect route.
 - In six of the cases, patients received or possibly received US-licensed Neulasta intramuscularly instead of subcutaneously.
 - Four cases reported patients who received US-licensed Neulasta intravenously instead of subcutaneously.
 - Six cases reported patient outcomes including decrease in neutrophil count, bone pain, chest pain, and hematoma. The remaining cases did not provide patient outcomes.
 - Contributing factors were not reported.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the route of administration is clearly listed. The route of administration information in the Prescribing Information for Ziextenzo is similar to the reference product and does not appear vulnerable to medication errors. Additionally, the proposed IFU for Ziextenzo depicts subcutaneous administration. Labeling revisions are not necessary at this time.

Incorrect storage (n = 8)

- Seven cases (FAERS Case No. 10778000, 11098586, 11457673, 3943611, 7885026, 9256234, 9690403) described incorrect storage of US-licensed Neulasta. The cases involved US-licensed Neulasta being stored outside of refrigeration. Contributing factors including leaving US-licensed Neulasta in the car, placing US-licensed Neulasta in the freezer, leaving outside (delivery), and storing outside of the refrigerator. Three of the cases reported that patients received US-licensed Neulasta that was improperly stored.
- One case (FAERS Case No. 8089474) reported possible incorrect storage of US-licensed Neulasta. The case reported that the dose of US-licensed Neulasta “did not work properly”. Per the reporter, a contributing factor is that US-licensed Neulasta may not have been stored properly during the transport along the supply line.

A review of Section 16 How Supplied/Storage and Handling of the Prescribing Information indicates that the storage information is clearly listed. Additionally, we recommend increasing the prominence of the storage information on the carton labeling to help mitigate the risk of this medication error.

Overdose (n = 4)

- Four cases (FAERS Case No. 8987095, 6944061, 6375877, 10521961) reported overdose errors.
 - o One case described a patient’s report of receipt of “a full month or four months of Neulasta in this single injection”. The patient reported fainting and abnormal WBCs. Contributing factors were not reported.
 - o One case reported that a patient received a full adult dose of US-licensed Neulasta. The reported stated that the patient should have received a dose modification due to “nadir labs”. Patient outcomes were not reported.
 - o In two cases, pediatric patients were incorrectly dispensed the entire contents of the US-licensed Neulasta PFS. One patient was administered the entire contents of the PFS and experienced elevated WBCs, decreased platelets and mild bone pain as a result of the error. The second patient was administered approximately half the contents of the PFS to achieve the intended dose of 3 mg. Per the reporter, excessive therapeutic response to dose administered indicates that a dosing error was possible.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the dosing information is clearly listed. Additionally, we note that the PI does not contain directives for dose modifications based on hematologic labs values. The dosing information in the Prescribing Information for Ziextenzo is similar to the reference product. However, we recommend that the Ziextenzo PI is updated to include the same dosing information for indications shared with the reference product US-licensed Neulasta and to inform users that Ziextenzo PFS cannot be used for the direct administration of doses less than 6 mg (0.6 mL).

Wrong technique (n = 3)

- Two cases (FAERS Case No. 8416674, 10777975) reported wrong technique in the drug usage process. Both cases described Neulasta being administered at an injection site other than those listed in the Prescribing Information. Contributing factors and patient outcomes were not reported.
- One case (FAERS Case No. 9871712) described a case in which a health care practitioner, who was administering Neulasta to a patient, "pulled back" on the US-licensed Neulasta plunger and blood appeared at the injection site. The patient's outcome was not reported.

A review of the proposed Instructions for Use for Ziextenzo indicates that the injection sites are clearly labeled and listed. We recommend changes to the IFU to increase clarity and readability and to help mitigate the risk of medication errors.

Dose omission (n = 2)

- Two cases (FAERS Case No. 6273409, 9256148) reported cases in which patients missed schedule doses of US-licensed Neulasta. The cases did not provide further details.

A review of Section 2 Dosage and Administration of the Prescribing Information indicates that the dose and frequency information is clearly listed. Label revisions are not necessary at this time.

Underdose (n = 2)

- Two cases (FAERS Case No. 11627353, 9256075) reported underdose errors. One case reported difficulty injecting the entire contents of the prefilled syringe as a contributing factor; the patient in that case did not experience adverse outcomes and returned later to receive the remainder of the dose. The remaining case did not provide contributing factors or patient outcomes.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the dosing information is clearly listed. The dosing information in the Prescribing Information for Ziextenzo is similar to the reference product. However, we recommend that the Ziextenzo PI is updated to include the same indications and dosing information as the reference product US-licensed Neulasta.

Wrong patient (n = 2)

- One case (FAERS Case No. 11627283) reported case in which a patient received a dose of Neupogen which was intended for another patient. The patient should have received US-licensed Neulasta. Contributing factors and patient outcomes were not reported.

- One case (FAERS Case No. 9256087) reported a case in which US-licensed Neulasta was administered to the wrong patient. Contributing factors and patient outcomes were not reported.

Labeling modifications are not necessary at this time.

Medication error (n = 1)

- One case (FAERS Case No. 5794099) reported a medication error involving US-licensed Neulasta. Further details were not provided.

This error did not provide details to fully interpret the case; therefore, labeling revisions are not warranted.

Wrong dose (n = 1)

- One case (FAERS Case No. 9256083) described a case in which a patient was on dose of 0.2 mL and 0.4 mL; however, the full US-licensed Neulasta prefilled syringe was dispensed. Therefore, it was unclear whether the actual doses received were accurate. The case did not report contributing factors or patient outcomes.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the dosing information is clearly listed. The dosing information in the Prescribing Information for Ziextenzo is similar to the reference product. However, we recommend that the Ziextenzo PI is updated to include the same indications and dosing information as the reference product US-licensed Neulasta. Additionally, we recommend that an improved Ziextenzo dosing device is developed to accommodate the direct administration of doses less than 6 mg (0.6 mL).

We excluded 76 cases because they described errors involving: the US-licensed Neulasta OnPro device (n = 27), name confusion with the proprietary name Neulasta (n = 21), errors not involving pegfilgrastim (n = 10), off label use (n = 6), duplicate reports (n = 3), wrong drug (n = 3), expired product errors (n = 2), unrelated literature report (n = 1), device malfunction with US-licensed Neulasta PFS (n = 1), product quality concerns with US-licensed Neulasta PFS (n = 1), and self-administration of an unprescribed product (n = 1).

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case Number	Manufacturer Control Number	FAERS Case Number	Manufacturer Control Number	FAERS Case Number	Manufacturer Control Number
6273409	US-AMGEN-KDL194291	8776703	US-AMGEN-USASP2012056682	8093450	US-AMGEN-USASP2011040854
9256148	US-AMGEN-USASP2012033729	9871756	US-AMGEN-USASP2013037619	8987095	US-AMGEN-USASP2012082547
10778000	US-AMGEN-USASP2014012826	9871776	US-AMGEN-USASP2014005309	6944061	US-AMGEN-KDL303823
11098586	US-AMGEN-USASP2015011473	7330371	US-AMGEN-KDL339668	9256070	US-AMGEN-USASP2012016639
11457673	US-AMGEN-USASP2015090215	7885017	US-AMGEN-KDL400721	9256189	US-AMGEN-USASP2012064963
3943611	US035894	7885071	US-AMGEN-KDL432148	9256242	US-AMGEN-USASP2012065128
7885026	US-AMGEN-KDL412600	8702433	Not reported	6375877	Not reported
8089474	US-AMGEN-USASP2011040381	7083087	US-AMGEN-QUU359140	11627353	US-AMGEN-USASP2015095835
9256234	US-AMGEN-USASP2012057800	10136263	US-AMGEN-USASP2014029976	9256075	US-AMGEN-USASP2012013258
9690403	US-AMGEN-USASP2013080410	10777995	US-AMGEN-USASP2014017176	11627283	US-AMGEN-USASP2015046989
10777949	US-AMGEN-USASP2014022803	11517529	US-AMGEN-USASP2015094289	9256087	US-AMGEN-USASP2012023927
11627136	US-AMGEN-USASP2014081624	11617255	US-AMGEN-USASP2015104232	8416674	US-AMGEN-USASP2012010237
5766272	US-AMGEN-US121053	7331621	US-AMGEN-KDL384006	10777975	US-AMGEN-USASP2014050259
5770507	US-AMGEN-US122453	8393053	US-AMGEN-USASP2012007495	10521961	Not reported
6597246	US-AMGEN-US212163	8435610	US-AMGEN-USASP2012012561	9256083	US-AMGEN-USASP2012023514
6597285	US-AMGEN-US232664	9256079	US-AMGEN-USASP2012022135	9871712	US-AMGEN-USASP2013010108
6597317	US-AMGEN-US221947	9256118	US-AMGEN-USASP2012049496		
6944160	US-AMGEN-KDL286632	9256194	US-AMGEN-USASP2012067109		
6944208	US-AMGEN-KDL277614	9256250	US-AMGEN-USASP2012082836		

6987263	US-AMGEN- QUU344715	5794099	US100455		
---------	------------------------	---------	----------	--	--

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁵ along with postmarket medication error data, we reviewed the following Ziextenzo labels and labeling submitted by Sandoz on August 27, 2015.

- Container label (syringe)
- Carton labeling (inner)
- Carton labeling (outer)
- Prescribing Information (not pictured)
- Instructions for Use (not pictured)

G.2 Label and Labeling Images

- Container label (syringe)



- Carton labeling (inner)

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EBONY A WHALEY
06/23/2016

LUBNA A MERCHANT
06/23/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 9, 2016

TO: Ann Farrell, M.D.
Director
Office of Hematology and Oncology Products (OHOP)
Division of Hematology Products (DHP)
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Review of EIR for Parexel International GmbH, Berlin, Germany covering BLA 761045 for LA-EP2006 (pegfilgrastim) sponsored by Sandoz, Inc.

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of Pharmacokinetic/ Pharmacodynamic study LA-EP06-101 at Parexel International GmbH, Berlin, Germany. No significant deficiencies were observed and no Form FDA 483 was issued. The final classification is No Action Indicated (NAI).

After review of the inspectional findings, I recommend that the data from the clinical portion of study LA-EP06-101 be accepted for further agency review.

Study Number: LA-EP06-101
Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US-registered) after single

dose subcutaneous application in healthy subjects"

Study Dates: June 24 - December 28, 2010

Clinical Site: Parexel International GmbH
Early Phase Clinical Unit
Spandauer Damm 130, D-14050
Berlin, Germany

The inspection of the clinical portion of study LA-EP06-101 was conducted by ORA investigator Marc A. Jackson at Parexel International GmbH, Berlin, Germany from March 7-11, 2016. The inspection included a review of the Independent Ethics Committee (IEC) approval process and correspondence, informed consent process, randomization and blinding, adverse events (AEs), concomitant medications, study sample processing and storage, test and reference article accountability, dispensation and storage, employee training, and SOPs. No significant discrepancies were observed and no Form FDA 483 was issued at the conclusion of the inspection. Reserve samples were collected and sent to CDER-DPA, St. Louis, MO.

This review is based on the draft Establishment Inspection Report (EIR). Upon receipt and review of the final endorsed EIR by OSIS, this review will be amended if the findings in the endorsed EIR warrant a change in the recommendations.

Recommendations:

Following review of the draft EIR, the data from the clinical portion of the audited study were found to be reliable. Thus, this reviewer recommends that the data from study LA-EP06-101 be accepted for further agency review.

Srinivas R. Chennamaneni, Ph.D.
DNDBE, OSIS

Final Classification:

Clinical Site

**NAI: Parexel International GmbH, Early Phase Clinical Unit,
Berlin, Germany**

FEI: 3008483972

CC:

OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Chennamaneni
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Stanley
OND/OHOP/DHP/Farrell/McMullen
ORAHQ/BIMO/Bukowczyk/Jackson

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Parexel International GmbH, Early Phase Clinical Unit,
Berlin, Germany/BLA 761045_LA-EP2006 (pegfilgrastim), 10 mg/mL

Draft: SRC 5/30/2016

Edit: GB 6/6/2016; CB 6/7/2016

OSI: **BE7016**

FACTS: 11600978

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRINIVAS RAO N CHENNAMANENI
06/09/2016

CHARLES R BONAPACE
06/09/2016

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 5/24/2016

From: Michael Shanks, OPQ/OPF/DIA
Patrick Lynch, Ph.D., OBP/DBRRII
Bo Chi, Ph.D., DMA/MABIV

To: BLA File, STN 761045/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of LA-EP2006 DS at the Sandoz GmbH facility in Kundl, Austria.

Applicant: Sandoz, Inc.

Facility: Sandoz GmbH
Biochemiestrasse 10
AT-6250 Kundl
Austria
FEI 3002806523

Product: LA-EP2006

Dosage: Injectable sterile, clear, and colorless solution for subcutaneous administration. Single use pre-filled syringe containing 6 mg/0.6 mL (10 mg/mL).

Indication: Therapeutic to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

Waiver Recommendation

BLA STN 761045/0 proposes manufacture of EP2006 (b) (4) at Sandoz GmbH, Kundl, Austria (FEI 3002806523), the pegylation of (b) (4) LA-EP2006 DS at Lek Pharmaceuticals d.d., Mengeš, Slovenia (FEI 3002807470), and LA-EP2006 DP at (b) (4). The proposed EP2006 (b) (4) manufacturing process, up to (b) (4) step, is identical to that of the EP2006 DS previously approved under BLA 125553 manufactured at Sandoz GmbH, Kundl, Austria.

The most recent inspection of the Sandoz GmbH was a comprehensive surveillance inspection conducted on 04/20-30/2015 for profiles BTP, CHG, CSN, CSS, CTX, POW, SPW, SVS, TCM, TTR, and CBI included evaluation of the Quality Systems, Facilities

and Equipment, Production, and Laboratory Control Systems supporting production of drug substances including biologically derived drug substances, sterile powders for injection, and solid oral dosage forms. This inspection was VAI and found acceptable. Additionally, a comprehensive surveillance and Pre-approval Inspection for **EP2006**, (**BLA 125553**) and Bexsero vaccine (BLA 125546) was conducted on 09/08-09/16/2014 and covered the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Systems for Profiles CBI, CSS, CTX, SPW, SVS, and VBP. This inspection was VAI and the facility was found to be compliant with CGMPs. .

Based on the compliance history of the firm, the current CGMP status, and the fact that Sandoz GmbH has been licensed to manufacture **EP2006 DS** (BLA 125553), and other biological products using similar manufacturing processes, it is recommended that the pre-license inspection of the Sandoz GmbH DS manufacturing facility in Kundl, Austria (FEI 3002806523) be waived for BLA 761045/0 (action date 06/26/2016).

Summary

BLA STN 761045/0 proposes manufacture of EP2006 (b) (4) at Sandoz GmbH, Kundl, Austria (FEI 3002806523), the pegylation of EP2006 (b) (4) (b) (4) DS at Lek Pharmaceuticals d.d., Mengeš, Slovenia (FEI 3002807470), and LA-EP2006 DP at (b) (4). This waiver recommendation is in regard to EP2006 (b) (4) manufacture at Sandoz GmbH.

Facility and Process Information

(b) (4)

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

The firm is registered as a human and veterinary drugs, and medical device manufacturer. Sandoz GmbH Kundl, Austria (Module 3) is currently licensed for manufacture EP2006 drug substance under BLA STN 125553/0. The last surveillance inspection on March 2016 covered 36 products and included a PLI to support the approval of BLA STN 761042/0 for Brelsina. The inspection prior to the most recent was conducted by ORA (PR/SEA-DO and PRL W) and CDER (BMAB/OC and DTP/OBP) from 9/8/2014 to 9/16/2014 covering the manufacture of EP2006 drug substance (and associated testing operations) under FDA application BLA STN 125553/0.


2. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

Previous inspections have encompassed profile classes BTP, CBI, CFS, CRU, CSN, CSS, CHG, CTL, CTX, POW, SPW, SVS, TCM, TTR and VBP, and in all cases have resulted in an acceptable NAI or VAI status.

3.  (b) (4)

As noted in the response to Question 1, Sandoz GmbH Kundl, Austria (Module 3) is currently approved for manufacture of EP2006 drug substance under BLA STN 125553.

4. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The proposed manufacturing scheme for EP2006  (b) (4) is identical to the currently approved manufacturing process for EP2006 drug substance under BLA STN 125553.

Signed:

Michael R. Shanks, OPF/DIABRI Reviewer _____ DATE _____

Patrick Lynch, Ph.D., OBP/DBRRII Reviewer _____ DATE _____

Bo Chi, Ph.D., DMA/MABIV Reviewer _____ DATE _____

Christopher Downey, Ph.D., OBP/DBRRII ATL _____ DATE _____

Patricia Hughes, Ph.D., DMA/MABIV Branch Chief _____ DATE _____

Zhihao (Peter) Qiu, Ph.D., OPF/DIABRI, Branch Chief _____ DATE _____

David Frucht, MD, DBRR II/OPB, Director _____ DATE _____



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 05/19/2016
To: Administrative File, STN 761045
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for **LA-EP2006**
US License: **2003**
Applicant: Sandoz, Inc.
Mfg Facility: Drug Substance:
Sandoz GmbH, Biochemiestrasse 10, Kundl, Austria FEI 3002806523
Lek Pharmaceuticals d.d., Kolodvorska 27, Mengeš, Slovenia FEI 3002807470
Drug Product:

(b) (4)

Product:
Dosage: Injectable sterile, clear and colorless solution for subcutaneous administration. Single use pre-filled syringe containing 6 mg/0.6 mL (10 mg/mL).
Indication: Therapeutic to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia..
Due Date: 06/26/2016

RECOMMENDATION: This application is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes the manufacture of LA-EP2006 Drug Substance and Drug Product at the Sandoz GmbH, Lek Pharmaceuticals d.d., and (b) (4). The starting material for the production is (b) (4).

The PAI at Sandoz GmbH for this application was waived. The drug substance process consisting of pegylation (b) (4) LA-EP2006 DS is manufactured at Lek Pharmaceuticals d.d. (Mengeš, Slovenia), a subsidiary of Sandoz. LA-EP2006 Drug Product is manufactured at the final fill finish site (b) (4) in the final

BLA 761045/0. LA-EP2006 DS and DP Manufacture

primary packaging (syringes). Sandoz GmbH releases the LA-EP2006 6 mg/0.6 mL solution for injection. In addition to the sites mentioned above in the manufacturer of LA-EP2006 6 mg/0.6 mL, Novartis Pharma AG, Lek Pharmaceuticals d.d. (b) (4)

(b) (4) perform testing of the DS and DP. A Pre-license inspection was conducted on 03/08 – 14/2016 at Lek Pharmaceutical d.d. No FDA Form 483 was issued, and a final recommendation of acceptable (NAI) has been made. A For Cause and Pre-license inspection was conducted on (b) (4) at (b) (4). A six-item FDA Form 483 was issued, and a final recommendation of acceptable (VAI) has been made. All other related DS and DP facilities have an acceptable compliance status.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S Drug Substance [Substance – Manufacturer]

3.2.S.2. Manufacture

3.2.S.2.1 DS Manufacturers.

The site proposed for LA-EP2006 Drug Substance manufacture, cell banking operations, and testing is presented below in Table 1.

Table 1. Proposed Sites for LA-EP2006 DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Sandoz GmbH	Biochemiestrasse 10 AT-6250 Kundl, Austria	3002806523	The EP2006 (b) (4) is manufactured and tested (according to current Good Manufacturing Practices - cGMP). Preparation of the WCB, and storage of the MCB and WCB.
Lek Pharmaceuticals d.d. (a Sandoz company)	Kolodvorska 27 SI-1234 Mengeš, Slovenia	3002807470	The LA-EP2006 drug substance (pegylated EP-2006) is manufactured by pegylation of the EP2006 (b) (4) tested and released (according to current Good Manufacturing Practices - cGMP). (b) (4) DS testing.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DS testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DS testing.

Reviewer Comment 1: The facilities for manufacture of LA-EP2006 DS are adequately described.

- **Prior Inspection History for DS Manufacturing and Testing Sites**

BLA 761045/0. LA-EP2006 DS and DP Manufacture

Sandoz GmbH (FEI 3002806523), EP2006 (b) (4) (unpegylated) manufacture, IPC and release testing. A comprehensive surveillance inspection conducted on 04/30/2015 for profiles BTP, CHG, CSN, CSS, CTX, POW, SPW, SVS, TCM, TTR, and CBI included evaluation of the Quality Systems, Facilities and Equipment, Production, and Laboratory Control Systems supporting production of drug substances including biologically derived drug substances, sterile powders for injection, and solid oral dosage forms. This inspection was VAI and found acceptable. Additionally, a comprehensive surveillance and Pre-approval Inspection for EP2006, BLA 125553, and BLA 125546 (Bexsero vaccine) was conducted on 09/16/2014 that covered the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Systems for Profiles CBI, CSS, CTX, SPW, SVS, and VBP. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470), LA-EP2006 drug substance manufacture by pegylation of the EP2006 (b) (4) IPC and release testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

(b) (4)

Novartis Pharma AG (FEI 3002807772), Drug Substance release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products: (b) (4) Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460), Drug Substance release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable. (b) (4)

(b) (4)

(b) (4)

(b) (4)

This inspection was VAI and found acceptable.

- **Current Prior Approval Inspection Decisions**

BLA 761045/0. LA-EP2006 DS and DP Manufacture

Sandoz GmbH (FEI 3010479596). DIA, DMA, and OBP waived a PLI for this facility because a PLI for EP2006 was conducted on 09/16/2014, and this justification was documented in the waiver memo . A District file review was requested and the site was found acceptable based on file review.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470). DIA, DMA, and OBP conducted a joint PLI for LA-EP2006 drug substance at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

(b) (4)

Novartis Pharma AG (FEI 3002807772) was approved based on the facility CTL profile.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

***Reviewer Comment 2:** A recommendation regarding the compliance status for the DS production and testing facilities associated with the manufacture of LA-EP2006 is acceptable.*

3.2.S.2.2 Overview of LA-EP2006 DS Manufacturing Operations Conducted at Sandoz GmbH and Lek Pharmaceuticals d.d.

(b) (4)

3.2.A. Appendices

BLA 761045/0. LA-EP2006 DS and DP Manufacture

3.2.A.1 Facilities and Equipment [Manufacturer – substance – Dosage Form – Product]

3.2.A.1 Sandoz GmbH Facility

➤ **2.1.1-2 Sandoz Manufacturing Facility**

(b) (4)



BLA 761045/0. LA-EP2006 DS and DP Manufacture

(b) (4)

DRUG PRODUCT FACILITIES

3.2.P Drug Product [Substance – Manufacturer]

3.2.P.2. Manufacture

3.2.P.2.1 DP Manufacturers.

The site proposed for LA-EP2006 Drug Product manufacture, cell banking operations, and testing is presented below in Table 12.

TABLE 12. Proposed Sites for LA-EP2006 DP Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
(b) (4)			LA-EP2006 6 mg/0.6 mL DP solution for injection is manufactured, tested, and packaged.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DP Bioactivity testing.
Sandoz GmbH	Biochemiestraße 10 6336 Langkampfen Austria	3004828473	DP stability testing.
Lek Pharmaceuticals d.d.	Kolodvorska Cesta 27 Mengeš, 1234 Slovenia	3002807470	DP testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DP testing.

Reviewer Comment 23: *The facilities for manufacture of LA-EP2006 DP are adequately described.*

BLA 761045/0. LA-EP2006 DS and DP Manufacture

- **Prior Inspection History for DS Manufacturing and Testing Sites**



Novartis Pharma AG (FEI 3002807772), Drug Product release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products: (b) (4) (b) (4) Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing. A comprehensive surveillance inspection conducted on 03/18/2014 for profiles CRU, CXA, and SVS included evaluation of the Quality, Production, Laboratory Control, Materials and Facility and Equipment Systems. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance Inspection was conducted on 03/16/2012 that covered the Quality, Production, Facilities & Equipment, and Laboratory Control Systems for Profiles SVS, CXA, CBI, CSN and TAM. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470), Drug Product release and stability testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460), Drug Product release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable. (b) (4)

(b) (4)
(b) (4)
(b) (4) This inspection was VAI and found acceptable.

BLA 761045/0. LA-EP2006 DS and DP Manufacture

• **Current Prior Approval Inspection Decisions**



Novartis Pharma AG (FEI 3002807772) was approved based on the facility profile and Laboratory Control Systems coverage.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing was approved based on the facility profile and Laboratory Control Systems coverage.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470). DAI, DMA, and OBP conducted a joint pre-approval inspection for LA-EP2006 drug substance (pegylated EP2006) that included Laboratory Control Systems at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

Reviewer Comment 24: *the compliance statuses for the DP production and testing facilities associated with the manufacture of LA-EP2006 are acceptable.*



BLA 761045/0. LA-EP2006 DS and DP Manufacture

(b) (4)

CONCLUSION

Adequate descriptions were provided for the Sandoz GmbH (FEI 3002806523) and Lek Pharmaceuticals d.d. (FEI 3002807470) LA-EP2006 Drug Substance facilities, and the (b) (4) LA-EP2006 Drug Product facility proposed for DS and DP manufacture. The proposed DS and DP manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

Michael R. Shanks -S
Digitally signed by Michael R. Shanks -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200140831
7, cn=Michael R. Shanks -S
Date: 2016.05.20 14:20:09 -04'00'

Michael Shanks
Biologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S
Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Zhihao Qiu -S,
0.9.2342.19200300.100.1.1=2000438274
Date: 2016.05.20 14:31:45 -04'00'

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: May 18, 2016

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): Ziextenzo (pegfilgrastim)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761045

Applicant: Sandoz Inc.

1 INTRODUCTION

On August 27, 2015, Sandoz Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761045 for Ziextenzo (pegfilgrastim) injection under Section 351(k) of the Public Health Service Act. With this application Sandoz Inc. seeks approval for Ziextenzo (pegfilgrastim) injection as a biosimilar product to approved BLA 125031 for Neulasta (pegfilgrastim). The Applicant seeks approval for the same indication for which the referenced product Neulasta (pegfilgrastim) is approved: to decrease the incidence of infection as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

On November 4, 2015, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Ziextenzo (pegfilgrastim) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Ziextenzo (pegfilgrastim) injection.

2 CONCLUSIONS

Due to outstanding deficiencies, DHP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NATHAN P CAULK
05/18/2016

BARBARA A FULLER
05/18/2016

LASHAWN M GRIFFITHS
05/19/2016

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 28, 2016

TO: Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: Inspection of [REDACTED] (b) (4)
[REDACTED] (LA-EP2006
[pegfilgrastim], a biosimilar to Neulasta®), sponsored
by Sandoz Inc.

Summary:

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of pharmacodynamic (PD) portions of the following clinical study conducted by [REDACTED] (b) (4)
[REDACTED]

Based upon the results of the inspection, we recommend that ANC and CD34+ PD data from study LA-EP06-101 be accepted for further Agency review.

Study Number: LA-EP06-101 ([REDACTED] (b) (4) report N-A-OTH-11-028)
Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US- registered) after single dose subcutaneous application in healthy subjects"

Page 2 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

Study Dates: June 24, 2010 through December 28, 2010

Inspection of pharmacodynamic data from this study was conducted by OSIS/DGDBE Pharmacologist Kara A. Scheibner at (b) (4)

The audit included a thorough examination of facilities and equipment, review of SOPs and training records, review of method validation and study records including correspondence, and interviews and discussions with (b) (4) management and staff.

Following inspection of the study, Form FDA-483 was not issued.

Note that separate review memos covering inspections at other sites are finalized in DARRTS.

Conclusion: Based on review of the establishment inspection report, we recommend that ANC and CD34+ data from study LA-EP06-101 be accepted for further agency review.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Final

(b) (4)

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Scheibner

OTS/OSI/DNDBE/Bonapace/Dasgupta

Draft: KAS 04/26/16

Edits: MFS 04/26/2016; JC 4/27/2016

OSI File#: (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ (b) (4)

FACTS: (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARA A SCHEIBNER
04/29/2016

SEONGEUN CHO
04/29/2016

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 28, 2016

TO: Ann Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: Inspection of (b) (4)
(b) (4) covering BLA 761045 (LA-EP2006
[pegfilgrastim], a biosimilar to Neulasta®), sponsored
by Sandoz Inc.

Summary:

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of **Pharmacokinetic (PK) portions** of the following clinical studies conducted by (b) (4)
(b) (4)

Based upon the results of the inspection, we recommend that **PK data** from studies LA-EP06-101 and LA-EP06-302 be accepted for further review. However, we could not exclude the possibility of interferences from hemolytic and/or lipemic matrix on the ability to accurately quantitate pegfilgrastim concentrations. The OCP reviewer should consider potential impacts of hemolysis and lipemia on accurate measurement of pegfilgrastim.

Study Number: LA-EP06-101 (b) (4) report N-A-OTH-11-028)

Page 2 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US- registered) after single dose subcutaneous application in healthy subjects"

Study Dates: June 24, 2010 through December 28, 2010

Study Number: LA-EP06-302 ((b) (4) report N-A-OTH-12-027)

Study Title: "Pivotal study in breast cancer patients investigating efficacy and safety of LA-EP2006 and Neulasta®"

Study Dates: March 5, 2012 through December 4, 2013

Inspection of the pharmacokinetic data from these studies was conducted by OSIS/DGDBE Pharmacologist Kara A. Scheibner at

(b) (4)

The audit included a thorough examination of facilities and equipment, review of SOPs and training records, review of method validation and study records including correspondence, and interviews and discussions with (b) (4) management and staff.

Following the inspection, Form FDA-483 was issued (Included in Firm's response; **Attachment 1**). Additional minor observations were discussed throughout the inspection, and at the inspection close-out meeting. We received a written response to the FDA-483 observations from (b) (4) on February 4, 2016 (**Attachment 1**). The FDA-483 observations, (b) (4) and our evaluation of the observations and responses follow.

(b) (4)

Page 6 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

(b) (4)



Conclusion: Based on the observations above, and (b) (4) response, this reviewer recommends that **Pharmacokinetic data** from studies LA-EP06-101 ((b) (4) report N-A-OTH-11-028) and LA-EP06-302 ((b) (4) report N-A-OTH-12-027) be accepted for further agency review. However, based on available data, a lack of

Page 7 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

matrix interference on the analysis of pegfilgrastim could not be assured. This reviewer recommends that the OCP reviewer consider the potential impact of hemolytic and lipemic matrix interference on the ability to accurately quantitate pegfilgrastim concentration.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Final

(b) (4)

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Scheibner

OTS/OSI/DNDBE/Bonapace/Dasgupta

Draft: KAS 03/01/16

Edits: MFS 03/01/2016; JC 4/27/2016

OSI: File#: BE7016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites/ (b) (4)

FACTS: (b) (4)

107 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARA A SCHEIBNER
04/29/2016

SEONGEUN CHO
04/29/2016

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 26, 2016

TO: Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

and

Hasan A. Irier, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: Inspection of (b) (4) covering
BLA 761045 (LA-EP2006 [pegfilgrastim], a Biosimilar to
Neulasta®), sponsored by Sandoz Inc.

Summary:

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of anti-drug antibody (ADA) and neutralizing antibody (NAb) portions of the following clinical studies conducted by (b) (4)

Based upon the results of the inspection, we recommend that results from ADA screening and confirmatory assay be accepted,

Page 2 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

but recommend reanalysis of results using a less stringent cut point (99 %). In addition, we recommend that titer data be carefully considered, because of the firm's current practices of repeat analysis and data reporting during the titer assays.

Study Number: LA-EP06-101
Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US- registered) after single dose subcutaneous application in healthy subjects"
Study Dates: ADA analysis: 12/1/10 through 2/22/11; NAb analysis: 2/21/11 through 2/25/11

Study Number: LA-EP06-301
Study Title: "A randomized, double-blind, parallel-group, multi-center Phase 3 comparative study investigating efficacy and safety of LA-EP2006 and Neulasta® (EU-licensed) in breast cancer patients treated with myelosuppressive chemotherapy"
Study Dates: ADA analysis: 8/26/13 through 5/14/14; NAb analysis: 3/26/15 through 4/2/15

Study Number: LA-EP06-302
Study Title: "Pivotal study in breast cancer patients investigating efficacy and safety of LA-EP2006 and Neulasta®"
Study Dates: ADA analysis: 12/18/13 through 2/10/14; NAb analysis: 2/20/15 through 4/23/15

Inspection of the immunogenicity data from these studies was conducted by OSIS/DGDBE Pharmacologists Kara A. Scheibner and Hasan A. Irier at (b) (4) from (b) (4)

The audit included a thorough examination of facilities and equipment, review of SOPs and training records, review of method validation and study records including correspondence, and interviews and discussions with (b) (4) management and staff.

Following inspection of the studies, Form FDA-483 was issued (**Attachment 1**). Additional minor observations were discussed throughout the inspection and at the inspection close-out meeting. We received a written response to the FDA-483 observations from (b) (4) on February 11, 2016 (**Attachment 2**). The Form FDA-483 observations, (b) (4) response, and our evaluation of the observations and responses follow.

Page 3 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

Please note that this review is for observations related specifically to BLA 761045. Some of the observations (e.g., 1a, 1b, 1c) included in the Form FDA-483 applied to studies in BLA 761042, which were reviewed in a separate memo that was finalized on 02/08/2016 under BLA 761042.

OBSERVATIONS

(b) (4)

Page 8 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

(b) (4)

Conclusion: Based on the observations above, and (b) (4) response, we recommend the following:

1. We recommend accepting ADA data from screening and confirmatory assays in studies LA-EP06-301 and LA-EP06-302 for further agency review. However, given that the confirmatory cut points used for LA-EP2006, EP2006, and PEG were at 99.9%, we recommend the data be reassessed using a 99% confidence level. This reanalysis may result in additional confirmed positive samples, and thus, the impact on overall study outcome should be assessed.
2. We recommend that the results of ADA titer analysis from studies LA-EP06-301 and LA-EP06-302 be scrutinized carefully by the Review Division. Due to the concerns described above on repeat analysis and data reporting, we cannot ensure that the final reported results accurately represent ADA levels present in study samples.
3. Please note that due to time constraints, the inspection did not cover a thorough review of validation and study data for NAb analysis.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Hasan A. Irier, Ph.D.
DGDBE, OSIS

Page 9 - BLA 761045, LA-EP2006, sponsored by Sandoz Inc.

Final

(b) (4)

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Scheibner

OTS/OSI/DNDBE/Bonapace/Dasgupta

Draft: KAS 04/26/16

Edits: MFS 4/26/2016; JC 4/28/2016

OSI: File#: (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites/ (b) (4)

FACTS: (b) (4)

154 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARA A SCHEIBNER
04/29/2016

SEONGEUN CHO
04/29/2016

CLINICAL INSPECTION SUMMARY ADDENDUM

Date	April 21, 2016
From	Anthony Orendia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief
To	Patricia Dinndorf M.D., Clinical Reviewer Albert Deisseroth, M.D., Ph.D., M.S., Clinical Team Leader Rachel McMullen, M.P.H., M.H.A., Regulatory Project Manager
BLA	761045
Applicant	U.S. Biopharmaceuticals Sandoz, Inc., a Novartis Company
Drug	Pegfilgrastim (LA-EP2006), (biosimilar product to approved Neulasta®)
NME	Yes (Priority Application)
Therapeutic Classification	Biosimilar-351k application
Proposed Indication	Febrile neutropenia
Consultation Request Date	November 12, 2015
Summary Goal Date	May 1, 2016
Action Goal Date	June 26, 2016
PDUFA Date	June 26, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For BLA 761045, four clinical sites (Drs. Mehta, Motan, Nagarkar, and Ratnavelu) were selected for audit and inspection. The contract research organization (CRO) (b) (4) was also inspected.

The preliminary classification for the inspections of Drs. Nagarkar and Ratnavelu, and the CRO, (b) (4) is No Action Indicated (NAI) based on communications with the field investigator. The final classification for the inspection of Dr. Mehta is Voluntary Action Indicated (VAI). The study data derived from these clinical sites and CRO are considered reliable in support of the requested indication.

The preliminary classification of the inspection of Dr. Motan's site is Official Action Indicated (OAI). The findings at Dr. Motan's site regarding predated ECGs and some medical visit records is unlikely to have a significant impact on evaluation of the primary efficacy endpoint or safety assessment, since there is no evidence that patients appeared to have been harmed. However, final regulatory classification of inspection findings is pending review of the inspection report and evidence collected by OSI.

Based on results of the clinical investigators and the contract research organization (CRO) (b) (4) inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the indication.

An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. BACKGROUND

Both filgrastim and pegfilgrastim are granulocyte colony stimulating factors (G-CSFs) that act on hematopoietic cells by binding to specific cell surface receptors. Post-binding, these G-CSFs stimulate proliferation, differentiation, and end cell functional activation. Pegfilgrastim is marketed in the US and European Union (EU) by Amgen Inc. (Neulasta®), and is indicated to reduce the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes).

Two clinical trials (LA-EP06-301 and LA-EP06-302) were submitted in support of the applicant's BLA. Four foreign clinical sites were selected for audit, since domestic data were insufficient. These sites were selected based upon geographic location (countries outside the U.S. with potentially different standards of care) and enrollment numbers.

Study LA-EP06-301

Study 301 was a randomized, double-blind, parallel-group, multi-center Phase 3 comparative study investigating efficacy and safety of LA-EP2006 (pegfilgrastim) and EU-authorized Neulasta. Patients with histologically proven breast cancer, who had an indication for neoadjuvant or adjuvant treatment with docetaxel, doxorubicin, and cyclophosphamide ["TAC"] chemotherapy were included in the study. The primary efficacy endpoint of this study was the mean duration of severe neutropenia (DSN) during Cycle 1 of chemotherapy, defined as the number of consecutive days in which a patient had an absolute neutrophil count less than $0.5 \times 10^9/L$.

This study was conducted from June 28, 2012 (first patient, first visit) through February 11, 2014 (6-month safety follow-up, last patient last visit). The study was conducted in six countries: Russia, Ukraine, Romania, India, Brazil, and Mexico. Three hundred seventy three (373) patients were screened and 316 were randomized.

Based on the sponsor's analysis, LA-EP2006 was demonstrated to be equivalent and non-inferior to Neulasta in terms of DSN. The mean DSN in Cycle 1 was 0.75 days in patients treated with LA-EP2006 and 0.83 days in patients treated with Neulasta. DSN ranged from 0 to 3 days (LA-EP2006) and from 0 to 4 days (Neulasta), respectively (Full Analysis Set (FAS set)).

Study LA-EP06-302

Study 302 was also a randomized, double-blind, parallel-group, multi-center Phase 3 comparative study investigating the efficacy and safety of LA-EP2006 (pegfilgrastim) and EU-authorized Neulasta. Patients with histologically proven breast cancer, who had an indication for neoadjuvant

or adjuvant treatment with docetaxel, doxorubicin, cyclophosphamide (TAC) chemotherapy were included in the study. The primary efficacy endpoint of this study was the mean duration of severe neutropenia (DSN) during Cycle 1 of chemotherapy, defined as the number of consecutive days in which a patient had an absolute neutrophil count less than $0.5 \times 10^9/L$.

This study was conducted from March 5, 2012 (first patient, first visit) through December 4, 2013 (last patient, last visit). The study was conducted in eight countries: Argentina, Chile, India, Malaysia, Puerto Rico, Russia, Spain, and the US. Three hundred fifty two (352) patients were screened and 308 were randomized.

Based on the sponsor's analysis, LA-EP2006 was demonstrated to be equivalent and non-inferior to Neulasta in terms of DSN. Overall, the mean DSN was slightly longer in patients allocated to LA-EP2006 (FAS, 1.36 ± 1.133 days) than in patients allocated to Neulasta (FAS, 1.19 ± 0.984 days). Maximum DSN was also higher in patients allocated to LA-EP2006 (FAS, 6.0 days) than in patients allocated to Neulasta (FAS, 4.0 days).

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
Ajay Mehta, M.D. Central India Cancer Research Institute, 11 Shankar Nagar, West High Court Road, Nagpur 440010, Maharashtra, India	Site #901 Protocol LA-EP2006-301 Subjects (See below) 15 Screened 14 Enrolled	February 22-26, 2016	Pending: Preliminary VAI
Doina Elena Ganea Motan, M.D., Ph.D. Spitalul Judetean de Urgenta "Sf. Ioan Cel Nou" Bdul. Nr. 21 Suceava, Jud. Suceava, 720237, Romania	Site #404 Protocol LA-EP2006-301 Subjects (See below) 14 Screened 10 Enrolled	February 22-25, 2016	Pending: Preliminary OAI
Rajnish Nagarkar, M.D. Curie Manavata Cancer Centre Nashik Maharashtra, 422004 India	Site #905 Protocol LA-EP2006-302 Subjects (See below) 7 Screened 6 Enrolled	March 14 - 18, 2016	Pending: Preliminary NAI
Kananathan Ratnavelu, M.D. NCI Hospital, 71800 Nilai, Negeri Sembilan Darul Khusus Malaysia	Site #404 Protocol LA-EP2006-302 Subjects (See below) 11 Screened 8 Enrolled	February 29 - March 4, 2016	Pending: Preliminary NAI

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
(b) (4)	CRO for: Protocol LA-EP2006-301 Subjects =316 Protocol LA-EP2006-302 Subjects =308	February 29 - March 3, 2016	Pending: Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator

1. Dr. Ajay Mehta, M.D./Study Protocol LA-EP2006- 301/Site #901

Maharashtra, India

The inspection was conducted from February 22 to 26, 2016. A total of 15 subjects were screened and 14 enrolled. Twelve patients completed the study; two study subjects died, thus, these were early terminations from the study. An audit of 14 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the conclusion of the inspection.

Specifically, five subjects (one episode each in Cycle #5 for Subjects 9, 11, 13, and 14, and two episodes in Cycles #5 and #6 for Subject 15) received recombinant human G-CSF products (commercial product/incorrect study drug) that were not allowed during the course of the study according to section 6.6.7 of the protocol.

Reviewer comments:

These findings were not considered critical, and were previously reported to the BLA. Further, Dr. Mehta explained in his response that the study drug product intended for administration had undergone a temperature excursion outside the allotted threshold and commercial product was administered to a limited number of subjects in later cycles.

Dr. Mehta's response to the List of Inspectional Observations on March 11, 2016 was considered adequate.

Notwithstanding the above isolated regulatory deficiency, data submitted by this clinical site appear acceptable in support of this specific indication.

2. Doina Elena Ganea Motan, M.D., Ph.D./ Study Protocol LA-EP2006- 301/Site #901
Suceava, Romania

The inspection was conducted from February 22 to 25, 2016. A total of 14 subjects were screened and 11 enrolled. Ten patients completed the study; one study subject withdrew consent after enrollment. An audit of 11 enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. There were protocol deficiencies related to ECGs. The protocol required that "the following test and/or data collection must be performed on Day 21 (\pm 3days) of Cycle 6," but this was not done for all subjects.

A Form FDA 483 (Inspectional Observations) was issued at the conclusion of the inspection and observations have been discussed with DHP.

Specifically, nine of 24 ECGs at the site were noted to have the headers containing date and time removed and hand written dates added. For four of the subjects' ECGs (Subjects (b) (6)) records in the site's cardiology department indicated that the ECGs had been performed on different dates (end of study) than the handwritten date (end of treatment) present on the ECG tracing indicated.

Reviewer comments:

During the inspection, the ORA investigator confirmed that these four subjects had ECGs performed at the institution's Department of Cardiology on the end of study visit day. Dr. Motan's response indicates that these ECGs had been predated by site staff who did not understand good clinical practice documentation practices. Additionally, Dr. Motan indicated that medical records of six subjects (including four subjects who also had pre-dated ECGs) had similarly been predated. Site staff was retrained on proper documentation and GCP procedures and the records were corrected appropriately to indicate the date procedures had actually been performed. The clinical investigator indicated that the site had a poor understanding of appropriate GCP

documentation practices and had predated these subjects' source documents. The findings related to predated ECGs are unlikely to have a significant impact on evaluation of the primary efficacy endpoint. No cardiac adverse events were reported for subjects enrolled at this site.

OSI is reviewing the inspection report and evaluating evidence included with the report. The inspectional observations noted above are based on communication with the field investigator, preliminary review of the EIR and Form FDA 483, and the clinical investigator's written response to the 483. The date documentation violations reported at this site are unlikely to impact assessment of the primary efficacy endpoint, and based upon review of adverse events data reported for this site, also no impact on subject safety from a cardiac standpoint. A clinical inspection summary addendum will be generated if conclusions change significantly upon receipt of the Establishment Inspection Report (EIR).

3. Rajnish Nagarkar, M.D./ Study Protocol LA-EP2006- 302/Site #905
Maharashtra, India

The inspection was conducted from March 14 to 18, 2016. A total of seven subjects were screened and six enrolled. Six subjects completed the study. An audit of seven screened subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Kananathan Ratnavelu, M.D./ Study Protocol LA-EP2006- 302/Site #404
Malaysia

The inspection was conducted from February 29 to March 4, 2016. A total of 11 subjects were screened and 8 enrolled. Seven patients completed the study; one study subject withdrew from the study after enrollment. An audit of 8 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR-CRO

(b) (4)

The inspection was conducted from (b) (4). This CRO inspection was needed to ensure that there were no monitoring concerns for this biosimilar application. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors; review of controls and security of electronic systems; and data collection and handling procedures; adequacy of monitoring and corrective actions taken by the sponsor/monitor for the studies; clinical site study personnel training in GCP, and memorandum documents and reporting updates to clinical site investigators regarding serious unexpected adverse events.

In general, this site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued at the end of the CRO inspection. No monitoring problems were found during the CRO inspection. Data submitted by this CRO appear acceptable in support of the requested indication.

{See appended electronic signature page}

Anthony Orendia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/Anne Farrell
Review Division /Medical Team Leader/Albert Deisseroth
Review Division/Medical Officer/Patricia Dinndorf
Review Division /Project Manager/Raquel McMullen
Review Division/MO/Anthony Orencia
OSI/Office Director/David Burrow (Acting)
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Anthony Orencia
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
04/21/2016

JANICE K POHLMAN
04/21/2016

KASSA AYALEW
04/21/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, Ophthalmic Device Branch (REGO)

Date: February 9, 2016

To: Patrick Lynch, CDER/OBP/DBRRII
Patrick.Lynch@fda.hhs.gov

Chris Downey, CDER/OBP/DBRRII
Christopher.Downey@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Rachel McMullen

Through: Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH

Viky Verna -S

Digitally signed by Viky Verna S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Viky Verna S,
0 9 2342 19200300 100 1 1=2000495623
Date: 2016.03.11 12:13:02 -0500

From: Crystal Lewis, REGO, DMQ, OC, CDRH

Applicant: Sandoz, Incorporated
100 College Road West
Princeton, NJ 08540
FEI#

Application # BLA761045

Consult # ICC#1500691

Product Name: LA-EP2006 (pegfilgrastim, proposed biosimilar to US-licensed Neulasta)

Pre-Approval Inspection: No

Documentation Review: Additional Information Required

Final Recommendation: **DELAY**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of BLA761045.

PRODUCT DESCRIPTION

LA-EP2006 is indicated for use with patients who have been diagnosed with non-myeloid malignancies who are receiving myelosuppressive anti-cancer drugs. The drug's proposed

indication is to decrease the incidence of infection that is associated with febrile neutropenia. The LA-EP2006 drug product is marketed as a single use combination product that consists of a pre-filled syringe and a needle safety device.

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:



Responsibility – The firm is responsible for the final assembly and packaging for the final combination product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on [REDACTED] (b) (4) The inspection covered drug GMP policies and was classified VAI.

Inspection Recommendation:

(1) An inspection is not required because:

- The firm has received a drug inspection which covered GMP requirements within the last two years. The inspection was acceptable therefore a preapproval inspection is not required.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

The firm's documentation for Management Control was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm's documentation for Design Control was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm's documentation for Purchasing Controls was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm's documentation for CAPA was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls

The firm's documentation for Production and Process Controls were not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.70.

Production Flow

The firm's documentation for Production Flow was not found.

Acceptance Activities

The firm's documentation for Acceptance Activities was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.80(b),(c),(d).

Documentation Review Recommendation

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of application LA-EP2006 (pegfilgrastim, proposed biosimilar to US-licensed Neulasta), BLA761045, in reference to applicable 21 CFR 820 regulations and (or) manufacturing of the finished combination product:

1. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.30, Design Controls. Specifically, your firm did not describe its design control system which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Your firm should also provide a copy or a summary of the plan used to design the combination product. Your firm should explain how it implemented the plan for the combination product project.
2. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.20, Management Controls. Specifically, the submission did not include information addressing which firm has ultimate responsibility for the overall combination product. The submission did not include a description of the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements). Please provide a description of your procedures for Management Controls.
3. The information provided by your firm has inadequately addressed the requirements of 21

CFR 820.50, purchasing controls. The submission did not specify the controls applicable to your firm's suppliers. This would include any contract design, service or contract manufacturers for the combination product under review. Please provide a description of your procedures for Management Controls. Please explain how your firm will ensure that changes made by contractors/suppliers will not affect the final combination product.

4. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.100, Corrective and Preventive Action (CAPA) System. Your firm did not provide any details or a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System. Please provide a description of your CAPA system and explain how it will ensure identification existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of nonconformance; and, verification or validation of the actions. Please explain how the CAPA system will communicate between facilities involved in the manufacturing of the combination product.

5. Please describe your procedures for receiving or incoming acceptance activities. The procedure(s) should include the extent the supplier has demonstrated a capability to provide products and services to meet your firm's specifications.

6. Please provide a summary of its procedures for final acceptance activities. These procedures should include specific release criteria such as sterilization and quarantine for finished combination products.

7. The information provided by your firm did not describe its production and process controls. Please provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product occurs, and how such conditions could affect the combination product.

8. The information provided did not describe the production flow for the combination product. Please provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

RECOMMENDATION

The approvability of application LA-EP2006 (pegfilgrastim, proposed biosimilar to US-licensed Neulasta) BLA761045 should be delayed for the following reasons:

- (1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

Crystal
Lewis -S

Digitally signed by Crystal Lewis -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Crystal Lewis -S,
0.9.2342.19200300.100.1.1=2000430
186
Date: 2016.03.11 12:34:53 -05'00'

Crystal Lewis

Prepared: CLewis: 02/09/16

Reviewed: VVerna:2/16/16; 3/11/16

CTS No.: ICC150691

BLA761045

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

Inspectional Guidance

Firm to be inspected:

Firm Name

Address

FEI:

CDRH recommends the inspection under the applicable Medical Device Regulations of Firm Name, located in City, Country (FEI # 12345).

OPTIONS:

(1) A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

(2) A limited inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the Combination product name (Application number).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

Yellow highlights: Delete

Gray fields: Fill-in

ALWAYS: DELETE WHAT DOES NOT APPLY

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Reviewer Name

Title,

Branch

Division

Office of Compliance, WO66 RM XXXX

Phone: 301-796-XXXX

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Branch Chief Name

Chief

Branch Name

Division

Office of Compliance, WO66 RM XXXX

Phone: 301-796- 5770

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL S MCMULLEN

03/23/2016

CDRH signed off on this ICC review memo on 3/11/16 and the Division received this on 3/11/16 from Crystal Lewis (CDRH OC reviewer).

EXHIBIT 11

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
125553Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM

To: File for Sandoz, Inc.'s 351(k) Application, BLA # 125553, Referencing Neupogen (filgrastim)

From: The CDER Exclusivity Board

Re: Exclusivity Expiry for Neupogen (filgrastim) BLA 103353

Date: June 26, 2014

The CDER Exclusivity Board (Board) was asked by the Therapeutic Biologics and Biosimilars Team (TBBT) in CDER's Office of New Drugs to determine if there is any unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Neupogen (filgrastim) (BLA 103353; Amgen, Inc.) that would prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Neupogen (filgrastim).

Section 351(k)(7)(A) of the PHS Act states that "approval of ... [a biosimilar application] may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a)." Section 351(k)(7)(B) of the PHS Act states that ... [a biosimilar application] may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a)." Section 351(k)(7)(C)(i) of the PHS Act states that "[s]ubparagraphs (A) and (B) shall not apply to a license for or approval of ... a supplement for the biological product that is the reference product."

After reviewing the record, the Board concludes that BLA 103353 for Neupogen (filgrastim) was first licensed by FDA under section 351(a) of the PHS Act on February 20, 1991. The product was indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. A supplement (no. 1036) that added acute myeloid leukemia as an indication was approved by FDA on April 2, 1998. Additional supplements for changes and updates to the approved labeling were approved between May 29, 2002, and September 13, 2013.

The dates that are 4 and 12 years after the date of first licensure of Neupogen (filgrastim) are February 20, 1995, and February 20, 2003, respectively. A licensure of a supplement does not trigger a separate period of exclusivity. Accordingly, section 351(k)(7) of the PHS Act does not prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Neupogen (filgrastim).

Cc: The Therapeutics Biosimilar Biologics Team, Office of New Drugs, CDER
Sandra Benton, Marlene Schultz-DePalo

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARLENE T SCHULTZ-DEPALO

12/30/2014

Memo entered into DARRTS on behalf of the CDER Exclusivity Board

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

BLA#: 125553 Supplement Number: 0 BLA Type (e.g. SE5): 351(k)

Division Name: OHOP/DHP PDUFA Goal Date: 3/8/2015 Stamp Date: 5/8/2014

Proprietary Name: Zarxio

Established/Generic Name: TBD

Dosage Form: 300 mcg PFS, 480 mcg PFS

Applicant/Sponsor: Sandoz, Inc

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

None

Number of indications for this pending application(s): 5

Indications:

1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation
4. Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
5. Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- ☐ Yes. Please proceed to Section D.
☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
☒ No. Please proceed to the next question.

BLA# 125553

Page 2

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?☐ Yes: (Complete Section A.)☒ No: Please check all that apply:☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)☒ Deferred for some or all pediatric subpopulations (Complete Sections C)☐ Completed for some or all pediatric subpopulations (Complete Sections D)☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)☒ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)☐ Necessary studies would be impossible or highly impracticable because:☐ Disease/condition does not exist in children☐ Too few children with disease/condition to study☐ Other (e.g., patients geographically dispersed): _____☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)☐ Justification attached.*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.***Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

BLA# 125553

Page 3

justification):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
 - ☐ Disease/condition does not exist in children
 - ☐ Too few children with disease/condition to study
 - ☐ Other (e.g., patients geographically dispersed): _____

*** Not meaningful therapeutic benefit:**

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	None	< 36 kg	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): Preliminary Protocol: 3/06/15 Final Protocol Submission: 6/06/15 Study Completion: 3/06/16 Final Report Submission: 6/06/16							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☒ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	≥36 kg	None	All studies using US-licensed Neupogen	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☒ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

Zarxio is a biosimilar candidate. US-licensed Neupogen is the reference product. Extrapolation of efficacy and safety of the drug product is based on the finding that the data submitted in the BLA provides for a determination of biosimilarity.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/20/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # N/A BLA # 125553	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Zarxio Established/Proper Name: filgrastim-sndz Dosage Form: 300 mcg/0.5 mL in single use prefilled syringe and 480 mcg/0.8 mL in single use prefilled syringe		Applicant: Sandoz Inc. Agent for Applicant (if applicable): N/A
RPM: Jessica Boehmer, Lara Akinsanya		Division: Division of Hematology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <div style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO) Date of check: </div> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>March 8, 2015</u> Previous actions (specify type and date for each action taken) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

NDA/BLA #
Page 2

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	N/A
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

NDA/BLA #
Page 3

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Approval: March 6, 2015
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (indicate date(s)) Review(s) (indicate date(s)) 	August 14, 2014 - Letter August 11, 2014 - Review
❖ Labeling reviews (indicate dates of reviews)	RPM: July 22, 2014 DMEPA: February 25, 2015 and December 23, 2014 DMPP/PLT: March 3, 2015 OPDP: February 17, 2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None CMC Labeling: March 4, 2015
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	July 22, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	Exclusivity Board Memo December 30, 2014
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECD/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

NDA/BLA #
Page 4

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> <input type="checkbox"/> If yes, Center Director's Exception for Review memo (indicate date) <input type="checkbox"/> If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (approvals only) <ul style="list-style-type: none"> Date reviewed by PeRC <u>February 18, 2015</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (do not include previous action letters, as these are located elsewhere in package)	March 4 (2), 3, and 2, 2015; February 27, 26 (2), 23, 20, 19, 17 (2), 13, 11, 6 (2), 4, and 3, 2015; January 29, 27, 21, 20, 13 (2), 9, and 6, 2015; December 27, 16, and 11, 2014; November 18 (2), 12, 10, and 7, 2014; October 31 (2), 29, 16, 9, 6, and 2, 2014; September 17, 2014; August 13, 5, 2014; July 22, 16, and 7, 2014; June 27, 25, 24, 20, 16, 11, 9, 4, 2014; May 29, 22, and 21, and 20, 2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	March 5, 2015; January 13, 2015; November 13, 2014
❖ Minutes of Meetings <ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (indicate date of mtg) Pre-NDA/BLA meeting (indicate date of mtg) EOP2 meeting (indicate date of mtg) Mid-cycle Communication (indicate date of mtg) Late-cycle Meeting (indicate date of mtg) Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs) 	<input checked="" type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> November 19, 2013 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 	<input type="checkbox"/> No AC meeting January 7, 2015
Decisional and Summary Memos	
❖ Office Director Decisional Memo (indicate date for each review) Division Director Summary Review (indicate date for each review) Cross-Discipline Team Leader Review (indicate date for each review) PMR/PMC Development Templates (indicate total number)	<input checked="" type="checkbox"/> None March 5, 2015 February 26, 2015 7
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> Clinical Team Leader Review(s) (indicate date for each review) Clinical review(s) (indicate date for each review) Social scientist review(s) (if OTC drug) (indicate date for each review) 	February 9, 2015 February 9, 2015 <input checked="" type="checkbox"/> None

Version: 1/5/2015

NDA/BLA #
Page 5

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	See February 9, 2015 Clinical Review, page 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	N/A
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) REMS Memo(s) and letter(s) (indicate date(s)) Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	November 26, 2014
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review Cosigned January 30, 2015 and September 11, 2014 Reviews
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review Cosigned January 30, 2015 and September 11, 2014 Reviews
Statistical Review(s) (indicate date for each review)	January 30, 2015 Clin Stats; January 30, 2015 CMC Stats; September 11, 2014 CMC Stats
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	February 5, 2015
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review - Cosigned January 29, 2015 Review
Clinical Pharmacology review(s) (indicate date for each review)	January 29, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	January 20, 2015; September 16, 2014; July 15, 2014

NDA/BLA #
Page 6

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	January 30, 2015
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	January 30, 2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No care
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review Cosigned February 10, 2015 Review
• Branch Chief/Team Leader Review(s) (indicate date for each review)	February 10, 2015
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	February 6, 2015 Amendment January 30, 2015
❖ Microbiology Reviews	
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	February 2, 2015 (DP) January 30, 2015 (DS)
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	CDRH: February 27, 2015; February 20, 2015 (2) Immunogenicity: January 30, 2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	See January 30, 2015 Product Quality Review, Page 6
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ³)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: March 5, 2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

³ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

NDA/BLA #
Page 7

❖ NDAs: Methods Validation <i>(check box only; do not include documents)</i>	N/A
--	-----

Day of Approval Activities

❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
• Finalize 505(b)(2) assessment	N/A
❖ For Breakthrough Therapy(BT) Designated drugs: • Notify the CDER BT Program Manager	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the "preferred" name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
03/06/2015

Memorandum

Date: March 5, 2015

From: Biological Product Naming Working Group

Subject: BLA 125553 (submitted under section 351(k) of the Public Health Service (PHS) Act)

To: File

FDA has determined that the use of a distinguishing suffix (“-sndz”) in the nonproprietary name for Sandoz, Inc.’s (Sandoz) Zarxio (filgrastim-sndz), a biosimilar product submitted in a 351(k) biologics license application (BLA), is necessary to distinguish this product from Neupogen (filgrastim). Neupogen (filgrastim) is the reference product for this 351(k) application, and is licensed under BLA 103353 held by Amgen, Inc.

Zarxio (filgrastim-sndz) is a human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology. Sandoz has requested licensure of Zarxio (filgrastim-sndz) for each of the indications previously approved for Neupogen (filgrastim). Specifically:

- to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever;
- to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia;
- to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation;
- to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and
- to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

FDA has concluded that a nonproprietary name for Sandoz’ product that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance. This nonproprietary name for Zarxio (filgrastim-sndz) indicates its relationship to Neupogen (filgrastim), and also indicates that the products are distinct. The use of this nonproprietary name containing a distinguishing suffix also is expected to reduce confusion among healthcare providers who,

based on their experience with small-molecule drugs and generic versions of those drugs, may consider use of the same nonproprietary name to mean that the biological products are interchangeable. Additionally, the placement of the identifier as a suffix should result in this biosimilar product and its reference product being grouped together, yet remaining distinguishable, in electronic databases to help health care providers identify these products. If Zarxio and Neupogen were to share the same proper name, this could increase the likelihood that a patient could receive a product different from what was intended to be prescribed and lead to medication errors.

FDA also has concluded that a nonproprietary name containing a distinguishing suffix will facilitate postmarketing safety monitoring by providing a clear means of determining which “filgrastim” product is dispensed to patients. Due to the fact that health care providers often use nonproprietary names instead of proprietary names when prescribing and ordering products, particularly in the settings in which filgrastim products are used, and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.

On February 6, 2015, FDA advised Sandoz that the nonproprietary name of Zarxio should contain a unique suffix attached with a hyphen to the core name “filgrastim.”¹ FDA advised that the nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should Sandoz’ 351(k) BLA be approved. FDA explained that its comments on the nonproprietary name for this product did not reflect the Agency’s decision on a general naming policy for biosimilar products. That general policy is still under consideration.² As a result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, FDA advised that it would work with Sandoz to minimize the impact this would have to Sandoz’ manufacture and distribution of this product, should it be licensed.

¹ FDA has previously incorporated distinguishing features in the nonproprietary names of biological products that contain drug substances related to those found in previously licensed products to help minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing avoid confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint. For example, FDA has used three-letter prefixes to distinguish Granix (tbo-filgrastim) from Neupogen (filgrastim) and Zaltrap (ziv-aflibercept) from Eylea (aflibercept).

² FDA also has received several citizen petitions directed to the nonproprietary naming of biosimilar products. The citizen petition submitted by Johnson & Johnson requests that FDA require biosimilar products to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars (see Docket No. FDA-2014-P-0077). The citizen petitions submitted by the Generic Pharmaceutical Association and Novartis request that FDA require biosimilar products to be identified by the same nonproprietary name as their reference products (see Docket Nos. FDA-2013-P-1153 and FDA-2013-P-1398). Although FDA is designating a proper name that contains a distinguishing suffix for Zarxio, FDA is continuing to consider the issues raised by these citizen petitions and the comments submitted to the corresponding public dockets with respect to establishing a general naming convention for biological products.

On February 14, 2015, Sandoz proposed the suffix “-sndz”, i.e., a suffix composed of four lowercase letters derived from the name Sandoz. FDA evaluated the proposed suffix “-sndz” and determined that it was unlikely to be a source of error: the suffix is distinct from the names of other drug substances, does not look similar to the names of other currently marketed products, and does not include any abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as another element on the prescription or order. In addition, the suffix does not make promotional representations with respect to safety or efficacy of this product.

FDA also considered whether a proper name that includes an abbreviation derived from the prospective license holder’s company name would be inconsistent with statutory requirements or FDA’s practices for naming biological products. A biological product’s proper name is not expressly described in the PHS Act or FDA’s regulations for biological products as nonproprietary, although FDA’s longstanding practice is to designate proper names that are nonproprietary in nature. Importantly, the largest portion of the proper name will be the “core” name for the drug substance. The core name (“filgrastim”) reflects the drug substance name adopted by the United States Adopted Name (USAN) Council for the reference product, which is, by definition, nonproprietary. The name as a whole communicates the relationship between biological products that share this “core” name, with the added identifier derived from the name of the prospective license holder to indicate that this is a distinct product. Thus, FDA considers the inclusion of a distinguishing suffix composed of four letters that also are contained within the name of the prospective license holder to not be inconsistent with the description of the proper name as nonproprietary.³

For these reasons, FDA agrees that Zarxio will be identified as “filgrastim-sndz.” This nonproprietary name containing the distinguishing suffix will be the proper name designated in the license.

³ We note that FDA’s regulations at 21 CFR 299.4(d) reference the 1985 USAN Guiding Principles, which do not expressly address the use of a suffix derived from the manufacturer name, but do contain general statements distinguishing the adopted name from trademarked names. In FDA’s view, “filgrastim-sndz” is not inconsistent with the USAN Guiding Principles because, as discussed above, the name as a whole is nonproprietary. Further, we conclude that 21 CFR 299.4(d) does not describe a process that FDA must apply in order to designate a proper name for a biological product under section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
03/05/2015

LEAH A CHRISTL
03/05/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125553

**ACKNOWLEDGE CORPORATE
ADDRESS CHANGE**

Sandoz Inc.
Attention: John M. Pakulski, RPh
Head US, Regulatory Affairs
US Biopharmaceuticals
100 College Road West
Princeton, NJ 08540

Dear Mr. Pakulski:

We acknowledge receipt on October 28, 2014, of your October 28, 2014 correspondence notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from

506 Carnegie Center Drive
Suite 400
Princeton, NJ 08540

to

100 College Road West
Princeton, NJ 08540

for the following Biologics License Application (BLA):

BLA 125553 for Zarxio (filgrastim-sndz).

We have revised our records to reflect this change.

Please cite the BLA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

BLA 125553
Page 2

If you have any questions, call me, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology
Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
03/04/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, March 04, 2015 5:32 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: FDA proposed minor edits to Zarxio PI and PPI/IFU - BLA 125553- biosimilar to Neupogen - response due noon March 5 (also officially submitted March 5)
Attachments: ZarxioPI_FDA_Edits_4Mar2015.docx; Zarxio_IFU_FDA_Edits_4Mar2015.docx
Importance: High

Dear John,

Please reference your BLA for EP2006, BLA 125553.

Please see attached revised draft of the PI and PPI/IFU. Please review the Agency's very minor changes/comments, outlined below:

PI: deleted a duplicated word in the pregnancy category of “pregnancy” and minor editorial revisions (all in tracked changes)

PPI/IFU: relocated “Step 13” above the enlarged figure for better flow (in tracked changes)

If you agree with all the proposed edits you should provide a clean version of the PI and PPI/IFU via email. Any additional edits should be in tracked changes. If you accept all changes please officially submit these to the BLA as final labeling.

Please provide the labeling to me via email and officially submit by **12:00 PM EST, March 5, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

26 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
03/04/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, March 03, 2015 6:03 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: FDA proposed edits to Zarxio PI and PPI/IFU - BLA 125553- biosimilar to Neupogen - response due noon March 4
Attachments: FDA_edits_Zarxio_PI_3Mar2015.docx; Zarxio_PPI_IFU_3Mar2015.docx
Importance: High

Dear John,

Please reference your BLA for EP2006, BLA 125553.

Please see attached revised draft of the PI and PPI/IFU. Please review the Agency's changes/comments and do the following to the same drafts:

- Accept all changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). If you agree with all the proposed edits you should provide a clean version of the PI. Any additional edits should be in tracked changes.

Please provide the labeling to me via email by **12:00 PM EST, Wednesday, March 4, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

34 Pages of Draft Labeling have been Withheld in Full as
B4(CCI/TS) Immediately Following this Page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
03/03/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Monday, March 02, 2015 5:38 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: Zarxio, BLA 125553 - PMRs and PMCs
Attachments: PMR-1_PMCs_2-3-4-5-6-7_2Mar2015.docx

Importance: High

Dear John,

The review team agrees with your edits to the PMCs 2, 3, and 7 received by email March 2, 2015. The review team also agrees with your edits to PMR-1 and PMCs 4,5, and 6, received by email February 27, 2015. Please see the attached minor edits proposed from FDA for PMCs 3 and 7. If you agree, please accept changes and officially submit the final versions of all PMR and PMCs: PMR-1, PMCs 2, 3, 4, 5, 6, and 7 to the BLA.

We ask you to submit both by email and officially to the BLA, **a copy of the PMR and PMC studies** to us (attached) **with a statement that you agree to perform the trials as described and within the timelines that you specify**. Please contact me if you have any questions.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

PMR 1

PMR - 1 PMR Description of study:	To develop a presentation that can be used to directly and accurately administer filgrastim-sndz to pediatric patients who weigh less than 36 kg requiring doses that are less than 0.3 mL (180 mcg), and conduct any necessary human factors studies to evaluate the ability of caregivers to measure the appropriate doses.		
PMR Schedule Milestones:	Preliminary Protocol Submission:		07/06/2015
	Final Protocol Submission:		09/06/2015
	Study Completion:		06/06/2016
	Final Report Submission:		09/06/2016

PMC 2

PMC - 2 PMC Description of study:	To enhance the control strategy of (b) (4) by development, validation, and implementation of an analytical method to assess (b) (4) concentration for release or in-process testing of Zarxio drug product		
PMC Schedule Milestone:	Final Report Submission:		
	Implementation of analytical test for release to assess (b) (4) concentration in the drug product:		05/2016
	Specifications will be set latest after testing of 20 commercial batches		05/2020
	The final study report(s) will be reported according to 21 CFR 601.12		

PMC 3

PMC - 3 PMC Description of	To confirm the stability of Zarxio (filgrastim-sndz) drug product in 5% glucose at concentrations ranging from 5 mcg/ml to 15 mcg/ml of		
-------------------------------	---	--	--

study:	Zarxio (filgrastim-sndz) , in the presence of 2 mg/ml human serum albumin, in glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Testing will include potency and sub-visible particles.		
PMC Schedule Milestone:	Final Report Submission:		05/2016
	The final study report(s) will be reported according to 21CFR601.12		

PMC 4

PMC - 4 PMC Description of study:	To re-adjust the ^{(b) (4)} bioburden limit of ^{(b) (4)} for the ^{(b) (4)} drug substance based on process capability from 10 batches of product.	
PMC Schedule Milestones:		
	Study Completion:	08/2017
	Final Report Submission:	Annual Report May, 2018

PMC 5

PMC - 5 PMC Description of study:	Establish bioburden and endotoxin action limits for ^{(b) (4)} after data from more than 10 ¹¹ batches are available and provide the limits in an Annual Report.	
PMC Schedule Milestones:		
	Study Completion:	03/2017
	Final Report Submission:	08/2017

¹⁾ In case that less than 10 batches are manufactured by the date set for study completion, a preliminary action limit for bioburden and endotoxin will be set and re-assessed as soon as required number of batches is available.

PMC 6

PMC - 6 PMC Description of study:	Conduct studies to support the worst-case hold times ^{(b) (4)} at scale from a microbiology perspective. Provide study results in an Annual Report.	
PMC Schedule Milestones:		

	Study Completion:	12/2015
	Final Report Submission:	Annual report 05/2016

PMC 7

PMC - 7 PMC Description of study:	To update the stability program for <u>Zarxio (filgrastim-sndz)</u> pre-filled syringe drug product to include the syringe force measurements glide force and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.	
PMC Schedule Milestone:	Final Report Submission:	
	For functional testing on the devices constituent parts of the combination product; Implementation of analytical test for stability and inclusion of functional tests in the post-approval stability commitment (with test frequency t0 and thereafter once a year until end of shelf life) on one commercial batch per strength: - Syringe freedom of movement inside the needle safety device: - Removability of the flag label - Activation of the needle safety device	Annual report 05/2016
	For break loose and glide force on the pre-filled syringes (combination product): - Implementation of analytical test for stability and inclusion of test in the post-approval stability commitment (with test frequency t0 and thereafter once a year until	Annual report 05/2016 05/2020

Deleted: EP2006

	end of shelf life) - Shelf life specification will be set and specification included in the post-approval stability commitment after testing of sufficient commercial batches (i.e. 10 batches each per 300 mcg/0.5mL and 480 mcg/0.8mL strength ¹⁾). The updated annual stability protocol including testing and acceptance criteria (specifications) will be reported according to 21CFR601.12	
--	--	--

¹⁾ In case that less than 10 batches each per 300 mcg/0.5mL and 480 mcg/0.8mL strength are manufactured and have reached end of shelf life by the date set for study completion, a preliminary action limit for break loose and glide force will be set and re-assessed as soon as required number of batches is available.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
03/02/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, February 27, 2015 3:38 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: Please respond: Information request and response to Feb 25 email Sandoz proposed edits to Proposed PMR and PMCs - BLA 125553 for EP2006: - due noon March 2nd
Attachments: PMCs_2_3_7_FDA_Edits_27Feb2015.docx
Importance: High

Dear John,

Please reference BLA 125553 for EP2006.

Please see the attached FDA proposed edits and comments regarding PMC-2, PMC-3, and PMC-7 in response to your February 25, 2015 email correspondence with proposed edits to the proposed PMR and PMCs.

Please also provide a response to the Information Request, below.

CMC Information Request:

1. You are committing to implement an analytical method to assess (b) (4) concentration for release or in-process testing of your product under PMC-2 and plan to submit the final report as an annual report. An annual report is not the appropriate reporting category for implementation and establishment of specifications for your drug product. Please refer to 21CFR 601.12 for appropriate reporting category. The reporting category may be determined at the time of submission.

The proposed date for submission of the final study report of May 2020 is acceptable.

2. PMC 3 refers to an in-use stability study for your product under the conditions described in the dilution section of your product labeling (section 2.5). Please note that the in-use stability study that we are requesting in PMC 3 may be conducted in a laboratory setting simulating clinical conditions and the conditions described in the dilution section of your product labeling. Additionally, the results of this study should be submitted according to 21 CFR 601.12. (b) (4)

3. We have the following comments regarding PMC-7:

- a) You are committing to implement functional testing for the device constituents of Zarxio drug product (syringe freedom of movement inside the needle safety device, removability of the flag label and activation of the needle safety device) and propose submission of the study report in the 2020 annual report. You also commit to implementing analytical testing for break loose and glide force of Zarxio pre-filled syringes and propose to submit the study report in the 2017 annual report. FDA requests submission of an updated annual stability protocol for Zarxio drug product that incorporates testing for the device constituents and analytical testing for break loose and glide force of Zarxio drug product by 2016. The updated stability protocol may be submitted

in the 2016 Annual report. The results of these tests conducted on commercial Zarxio batches should be submitted within annual reports.

You propose to implement shelf life specifications (acceptance criteria) for functional testing of the device components and analytical testing of break loose and glide force and include them in the post-approval stability commitment after 10 batches each per 300 mcg/0.5 ml and 480/0.8 ml strengths are manufactured. The proposed testing frequency for these tests is at time zero and thereafter once a year until the end of shelf life. You plan to submit the study report in the

The updated stability protocol that includes acceptance criteria for the above referred tests should be submitted according to 21 CFR 601.12 by May 2020.

Please respond to the information request and proposed edits to the PMCs via email by **12:00 PM March 2, 2015**. Please also officially submit this information to your BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

PMC 2

PMC - 2 PMC Description of study:	To enhance the control strategy of (b) (4) by development, validation, and implementation of an analytical method to assess (b) (4) concentration for release or in-process testing of Zarxio drug product	
PMC Schedule Milestone:	Final Report Submission: <u>Implementation of analytical test for release to assess (b) (4) concentration in the drug product.</u> <u>Specifications will be set latest after testing of 20 commercial batches</u> <u>The final study report(s) will be reported according to 21 CFR 601.12</u>	<u>05/2016</u> <u>05/2020</u>

Deleted: (b) (4)

Deleted:

PMC 3

PMC - 3 PMC Description of study:	To confirm the stability of Zarxio drug product in 5% glucose at concentrations ranging from 5 mcg/ml to 15 mcg/ml of Zarxio, in the presence of 2 mg/ml human serum albumin, in glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Testing will include potency and sub-visible particles.	
PMC Schedule Milestone:	Final Report Submission: <u>The final study report(s) will be reported according to 21 CFR 601.12</u>	<u>05/2016</u>

Deleted: (b) (4)

Deleted:

Deleted: (b) (4)

Deleted:

PMC 7

PMC - 7 PMC Description of study:	To update the stability program for EP2006 pre-filled syringe drug product to include the syringe force measurements glide force and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.	
PMC Schedule Milestone:	<p>Final Report Submission:</p> <p><u>For functional testing on the devices constituent parts of the combination product on one commercial batch with testing frequency after production (10) and thereafter once a year until end of shelf life.</u></p> <p><u>- Syringe freedom of movement inside the needle safety device:</u></p> <p><u>- Removability of the flag label</u></p> <p><u>- Activation of the needle safety device</u></p> <p><u>For break loose and slide force on the pre-filled syringes (combination product):</u></p> <p><u>- Implementation of analytical test for stability and inclusion of test in the post-approval stability commitment (with test frequency 10 and thereafter once a year until end of shelf life)</u></p> <p><u>- Shelf life specification will be set and specification included in the post-approval stability commitment after testing of sufficient commercial batches (i.e. 10 batches each per 300 mcg/0.5mL and 450 mcg/0.5mL strength).</u></p> <p><u>The updated annual stability protocol including testing and acceptance criteria</u></p>	<p><u>Annual report 05/2016</u></p> <p><u>Annual report 05/2016</u></p> <p><u>05/2020</u></p>

Deleted: (b) (4)

Deleted: (b) (4)

Deleted:

Deleted: (b) (4)

	(specifications) will be reported according to <u>21CFR601.12</u>	
--	--	--

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/27/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, February 26, 2015 5:25 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: Please respond: BLA 125553 for EP2006: Response to Feb 25 email Sandoz proposed edits to Proposed PMR and PMCs - due February 27
Attachments: PMR_1_BLA_125553.docx; PMC_4_BLA_125553.docx; PMC_5_6_125553.docx
Importance: High

Dear John,

Please reference BLA 125553 for EP2006.

Please see the attached FDA proposed edits and comments regarding PMR-1, PMC-4, PMC-5, and PMC-6 in response to your February 25, 2015 email correspondence with proposed edits to the proposed PMR and PMCs. Additional FDA comments regarding PMC-2, PMC-3, and PMC-7 will be forthcoming.

Please respond via email by **4:00 PM February 27, 2015**.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

PMR 1

PMR - 1 PMR Description of study:	To develop a presentation that can be used to directly and accurately administer filgrastim-sndz to pediatric patients who weigh less than 36 kg requiring doses that are less than 0.3 mL (180 mcg), and conduct any necessary human factors studies to evaluate the ability of caregivers to measure the appropriate doses.	
PMR Schedule Milestones:	Preliminary Protocol Submission:	06/06/2015
	Final Protocol Submission:	09/06/2015
	Study Completion:	06/06/2016
	Final Report Submission:	09/06/2016

Comment [A1]: To Applicant: FDA does not agree with your proposed timeframes for the PMR milestones (b) (4) from the time originally proposed by FDA. We advise you to submit a preliminary protocol to assess both of the two options you have proposed. Depending on the option you choose, you can contact FDA to renegotiate the other milestone dates based on the need to refine the protocol and the availability of representative samples for testing.

Deleted	(b) (4)
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	
Deleted	

PMC 4

PMC - 4 PMC Description of study:	To re-adjust the ^{(b) (4)} bioburden limit of ^{(b) (4)} for the ^{(b) (4)} drug substance based on process capability from 10 batches of product.	
PMC Schedule Milestones:		
	Study Completion:	<u>03/2017</u>
	Final Report Submission:	<u>Annual Report</u> <u>May, 2018</u>

Deleted:

Deleted: (b) (4)

Formatted: Font: Bold

Formatted: Font: Bold

Deleted: (b) (4)

Deleted:

PMC 5

PMC - 5 PMC Description of study:	Establish bioburden and endotoxin action limits for (b) (4) after data from more than <u>10</u> batches are available and provide the limits in an Annual Report.	
PMC Schedule Milestones:		
	Study Completion:	<u>03/2017</u>
	Final Report Submission:	<u>05/2017</u>

Deleted:

Deleted:

Deleted:

Deleted:

Deleted:

Deleted:

PMC 6

PMC - 6 PMC Description of study:	Conduct studies to support the worst-case hold times (b) (4) at scale from a microbiology perspective. Provide study results in an Annual Report.	
PMC Schedule Milestones:		
	Study Completion:	<u>15/2015</u>
	Final Report Submission:	<u>Annual report</u> <u>05/2016</u>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/26/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, February 26, 2015 11:56 AM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: CMC Labeling Information Request - BLA 125553- biosimilar to Neupogen - due Feb 27

Importance: High

Dear John,

Please reference BLA 125553 for Zarxio (filgrastim-sndz). Please provide a response to the Information Request, below.

[CMC Labeling Information Request:](#)

We have the following comment regarding your revised carton labeling submitted on February 24, 2015.

A. All Carton Labeling

1. Add the statement “No U.S. Standard of Potency” to the bottom panel, per 21 CFR 610.61(r).

Please provide revised carton labels to me by email and officially submit them to the BLA by **12:00 PM, February 27, 2015.**

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/26/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Monday, February 23, 2015 4:24 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: Information Request - BLA 125553- biosimilar to Neupogen - due Feb 25

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

Information Request:

Submit an amendment to your 351(k) BLA to include information found in the “action package” for the Neupogen BLA (see draft guidance on Biosimilars: Questions and Answers Regarding Implementation of the BPCI Act, Q+A I.13). For your convenience, your amendment may provide a Web link to the SBA and FDA reviews currently available at Drugs@FDA, accompanied by a list of the documents that you intend to reference (identified by title and date), and this information will be incorporated by reference into your 351(k) BLA.

Please respond to me via email and officially submit your response to the BLA by **4:00 PM ET February 25, 2015**.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/23/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, February 20, 2015 3:42 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: Proposed PMR and PMCs - BLA 125553- biosimilar to Neupogen

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

As we continue our review of your application, our normal policy is to consider post-marketing studies and labeling at this time, in order to gain agreement in advance of an action date. We have determined that the following studies are necessary as post-marketing commitments (PMCs) or post-marketing requirements (PMRs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies are intended to describe the main objective and study characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key elements. It is also necessary for you to provide schedule milestone dates as indicated. Most milestones only require the applicant to provide the month and year for completion of each category (however, PREA milestones require month, day, and year). For milestone calculation purposes only, assume that an approval occurs on the BsUFA action date. Please note that we have provided proposed milestones for the PREA PMR per normal policy. We are available to discuss by teleconference, if needed.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMC and PMR studies description to us with a statement that you agree to perform the studies as described and within the timelines that you specify for the studies.

Final PMC and PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For PMR/PMCs, reply to our drafts as soon as possible, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document submitted by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all of the track changes edits that FDA has proposed with which you agree.
2. Assuming and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMCs and PMRs agreed upon. We ask the following:
 - a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

- b. Send the RPM an email courtesy copy of the draft version of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you by FDA that you agree with, and only return to us YOUR edits in track changes.
- c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR/PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

PMR - 1 PMR Description of study:	To develop a presentation that can be used to directly and accurately administer filgrastim-sndz to pediatric patients who weigh less than 36 kg requiring doses that are less than 0.3 mL (180 mcg), and conduct any necessary human factors studies to evaluate the ability of caregivers to measure the appropriate doses.	
PMC Schedule Milestones:	Preliminary Protocol Submission:	03/06/2015
	Final Protocol Submission:	06/06/2015
	Study Completion:	03/06/2016
	Final Report Submission:	06/06/2016

PMC - 2 PMC Description of study:	To enhance the control strategy of [REDACTED] development, validation, and implementation of an analytical method to assess [REDACTED] concentration for release or in-process testing of Zarxio drug product	
PMC Schedule Milestone:	Final Report Submission:	MM/YYYY

PMC - 3 PMC Description of study:	To confirm the stability of Zarxio drug product in 5% glucose at concentrations ranging from [REDACTED] mcg/ml to 15 mcg/ml of Zarxio, in the presence of 2 mg/ml human serum albumin, in glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Testing will include potency and sub-visible particles.	
PMC Schedule Milestone:	Final Report Submission:	MM/YYYY

PMC - 4 PMC Description of study:	To re-adjust [REDACTED] bioburden limit of [REDACTED] for the [REDACTED] drug substance based on process capability from 20 batches of product.	
--------------------------------------	---	--

PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 5 PMC Description of study:	Establish bioburden and endotoxin action limits for (b) (4) after data from more than 20 batches are available and provide the limits in an Annual Report.
--------------------------------------	--

PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 6 PMC Description of study:	Conduct studies to support the worst-case hold times (b) (4) at scale from a microbiology perspective. Provide study results in an Annual Report.
--------------------------------------	---

PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 7 PMC Description of study:	To update the stability program for EP2006 pre-filled syringe drug product to include the syringe force measurements glide force and injection force and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.
--------------------------------------	---

PMC Schedule Milestone:	Final Report Submission:	MM/YYYY
-------------------------	--------------------------	---------

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/20/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, February 19, 2015 5:17 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: FDA Advice and proposed edits to labeling - BLA 125553- biosimilar to Neupogen - response due noon Feb 20
Attachments: FDA_edits_Zarxio_PI_track_change_Feb19_2015.docx
Importance: High

Dear John,

Please reference your BLA for EP2006, BLA 125553.

The nonproprietary name of your product should contain a distinguishing suffix. FDA agrees with your proposed nonproprietary name, filgrastim-sndz, for your product. The nonproprietary name containing the distinguishing suffix will be the proper name designated in the license should your 351(k) BLA be approved.

FDA's comments on the nonproprietary name for this product do not reflect the Agency's decision on a general naming policy for biosimilar products. That general policy is still under consideration. As result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, we would work with you to minimize the impact this would have to your manufacture and distribution of this product, should it be licensed.

Revise the nonproprietary name to filgrastim-sndz wherever it appears in the proposed labels and labeling for your product.

Please see attached revised draft of the PI. Additional FDA comments regarding the PPI/IFU will be forthcoming.

Please review the Agency's changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). Do not officially submit the revised labeling at this time.

Please provide a revised labeling to me via email by **noon Friday, February 20, 2015**.

These are the Agency's preliminary revisions, and there may be additional proposed revisions during continued labeling discussions.

Please confirm receipt of this message.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

42 Pages of Draft Labeling have been Withheld in
Full as B4(CCI/TS) Immediately Following this Page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/19/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, February 17, 2015 9:38 AM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: DMEPA Information Request - BLA 125553- biosimilar to Neupogen - due Feb 17

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[DMEPA Information Request:](#)

Please provide your response to me by email by **4:00 PM ET today, February 17, 2015.**

We continue to recommend to better differentiate between the 300 mcg/0.5mL and 480 mcg/0.8mL strengths of the product to help prevent wrong strength selection errors. Per revised container labels and carton labeling, the only difference between the strengths of the product is the use of a blue color for 300 mcg/0.5mL and grey for 480 mcg/0.8mL which is insufficient differentiation. The remainder of the labels and labeling appear very similar. Additionally, using the same (b) (4) color for the proprietary name for 300 mcg/0.5mL and 480 mcg/0.5mL strengths adds to the similarity between the labels and labeling.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/17/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, February 17, 2015 10:48 AM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: CMC Labeling Information Request - BLA 125553- biosimilar to Neupogen - due Feb 17

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

CMC Labeling Information Request:

BLA 125553/0
Zarxio (filgrastim-bflm^[1])
Container Label and Carton Labeling Comments

We have the following comments regarding your revised container labels and carton labeling emailed on February, 11, 2015.

A. All Syringe Container Labels, Blister Foil and Tray and Carton Labeling

1. Ensure the font size of “filgrastim-bflm” is at least half the size font size of the proprietary name “Zarxio” per 21 CFR 201.10. Currently, the font size of “filgrastim-bflm” is less than half the size of “Zarxio.”
2. Relocate the dosage form to appear directly under “filgrastim-bflm.” To further clarify, the proper name for CDER-regulated biological products should not include the finished dosage form. The finished dosage form, injection, can appear on the line below the proper name.^[2] For the small syringe container label, omission of the dosage form is acceptable.
3. Relocate “MFD” (manufacturing date) away from the lot and expiration date and other important information on the label to avoid potential for confusion.

B. Blister Foil Labeling 1-Pack of 300 mcg and 480 mcg strengths

1. Relocate the NDC from under the strength statement to the top of the principal display panel above the strength statement, similar to the 10-count blister foil labeling, per 21 CFR 201.2.

^[1] Note that we are using “filgrastim-bflm” as a placeholder nonproprietary name in the comments. We acknowledge the continued discussion between Sandoz and the FDA with regard to the nonproprietary name. The nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should your 351(k) BLA be approved.

² Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. April 2013. Draft Guidance. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Please provide your response to me by email by **4:00 PM ET today, February 17, 2015.**

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

^[1] Note that we are using “filgrastim-bflm” as a placeholder nonproprietary name in the comments. We acknowledge the continued discussion between Sandoz and the FDA with regard to the nonproprietary name. The nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should your 351(k) BLA be approved.

^[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. April 2013. Draft Guidance. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/17/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, February 13, 2015 1:42 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: CMC Information Request - BLA 125553- due Feb 20

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below:

[CMC Information Request:](#)

Please provide your response to me by email by **12:00 PM ET, February 20, 2015.**

You provided freeze/thaw testing results from six process validation batches of EP2006 drug product manufactured by the proposed commercial process. The results indicate that



Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/13/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, February 11, 2015 4:30 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: RE: CDRH Information Request - BLA 125553- biosimilar to Neupogen - due Feb 16

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[CDRH Information Request:](#)

Please provide your response to me by email by **2:00 PM ET, February 16, 2015.**

In your response to the Agency information request dated February 6, 2015, you committed to implementing additional testing to assess device constituent part functionality of the combination product. You proposed that these tests would not be incorporated into ongoing stability assessments, but rather will be provided within future annual reports. To support this determination, you stated that “test methods are not yet fully developed and implemented, they are not included in the stability protocol in [Module 3.2.P.8.2]. These tests are not part of the shelf life specification”. The Agency notes that information provided within Module 3.2.P.8.3 of your submission does assess gliding force measurements for the combination product. Please include assessment of gliding force measurements within the shelf life specification for the combination product and update the Post-approval Stability Protocol and Stability Commitment to include this change.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/11/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, February 06, 2015 1:30 PM
To: Pakulski, John
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: CDRH Information Request - BLA 125553- biosimilar to Neupogen - due Feb 9

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[CDRH Information Request:](#)

Please provide your response to me by email by **4:00 PM ET, February 9, 2015.**

In your January 30, 2015 submission to BLA125553, you provided a *Post-approval Stability Protocol and Stability Commitment* to evaluate the drug constituent part of the combination product. We note that the proposed assessment does not appear to explicitly challenge the functionality of the device constituent parts of the combination product after exposure to aging. Revise this *Post-approval Stability Protocol and Stability Commitment* to evaluate essential performance of the device constituent parts of your combination product, including examinations of glide forces and activation of the needle safety device.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/06/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125553

GENERAL ADVICE

Sandoz Inc.
Attention: John M. Pakulski, RPh
Head, US Biopharmaceutical Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for EP2006.

We also refer to your May 8, 2014 and January 22, 2015, submissions containing draft carton and container labels and draft labeling text.

We have reviewed the referenced material and have the following comments and recommendations:

- A. The nonproprietary name of your product should contain a unique suffix. The suffix is intended to uniquely identify your product, and is not intended to convey any meaning. FDA recommends that the nonproprietary name of your product be filgrastim-bflm. While FDA recommends "bflm" as the suffix, you may also consider "dtsm" or "zbdm" as acceptable alternatives. Note that we are using filgrastim-bflm as the recommended nonproprietary name in the comments below. The nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should your 351(k) BLA be approved.

If you choose to propose an alternate suffix, notify the Regulatory Project Manager prior to any submission. However, please note that additional time would be needed for FDA to review and confirm the acceptability of the proposed suffix.

FDA's comments on the nonproprietary name for this product do not reflect the Agency's decision on a general naming policy for biosimilar products. That general policy is still under consideration. As result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, we would work with you to minimize the impact this would have to your manufacture and distribution of this product, should it be licensed.

BLA 125553
Page 2

- B. Revise the nonproprietary name to filgrastim-bflm wherever it appears in the proposed labels and labeling for your product.

We have the following comments regarding your proposed container labels and carton labeling submitted on May 8, 2014.

C. All Syringe Container Labels, Blister Foil and Tray and Carton Labeling (300 mcg/0.5 mL and 480 mcg/0.8 mL)

1. The nonproprietary name should be displayed in a contiguous manner using the same font size, weight, and color on all container and carton labeling as "filgrastim-bflm". Please also ensure the font size of filgrastim-bflm is at least half the size font size of the proprietary name "Zarxio" per 21 CFR 201.10.
2. Change the (b) (4) font color of the letter "O" in "ZARXIO" to match the color currently used for the letters in "ZARXI." We recommend this change to improve the readability of the product's name and reduce the likelihood of confusing "ZARXIO" with "Zarxi O", "Zarxi 0," or "Zarxi."
3. Consider capitalizing only the first letter of the proprietary name followed by lower case letters (i.e. "Zarxio" instead of "ZARXIO") as discussed in Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. Draft Guidance.
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>
4. Revise the color fonts utilized in the strength presentation to provide better differentiation between 300 mcg and 480 mcg strengths. Currently, the 300 mcg strength uses a blue (b) (4) color font to display the strength and the 480 mcg strength uses a grey color font. Thus, the two strengths are not adequately differentiated from each other, which can lead to wrong strength selection errors. See Guidance referenced in comment A.3.
5. Revise the dosage form statement located underneath the expression of strength, (b) (4) to "injection" in accordance with United States Pharmacopeia (USP) 12/1/14-4/30/15, USP 37/NF 32, General Chapter, Injection <1>, Nomenclature and Definitions, which FDA generally applies to determine appropriate dosage form terms. Additionally, revise the font size of the dosage form "injection" to be identical to the font size you plan to use to display filgrastim-bflm.

6. Relocate the dosage form to appear directly under filgrastim-bflm. For the small syringe container label, the dosage form may be omitted (see comment E.2.).
7. Clarify the meaning of "MFD" that appears on the side panels with the Lot and EXP.

D. Carton Labeling for 10-Pack of 300 mcg and 480 mcg strengths

1. Add the appropriate warning to the principal display panel (PDP) for devices that contain natural rubber with regard to Natural Rubber Latex (NRL) vs. Dry Natural Rubber (DNR) per FDA Guidance: User Labeling for Devices that Contain Natural Rubber (21 CFR 801.437).

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070929.pdf>

2. Revise the route of administration statement [REDACTED] (b) (4) " to read "For Subcutaneous Use or Intravenous Use Only".

3. Add the statement "Single-Use Only" to the PDP directly below the route of administration statement.

4. Remove the following statement from the side panel, [REDACTED] (b) (4) [REDACTED] since the PDP states the carton contains "10 prefilled syringes with a needle safety guard." We recommend removing this statement to provide clarity and reduce the likelihood with confusion regarding the correct net quantity provided in the carton.

5. Consider adding the following statement to the PDP:

"Refrigerate. Do Not Freeze"

We recommend this revision based on post marketing data related to wrong storage of similar products using the same delivery method.

6. Revise manufacturing information to comply with per 21 CFR 600.3(t), 21 CFR 610.61. For example:

"Manufacturer:" or "Manufactured by:" (Licensee or Applicant on the 356h form)

Sandoz

Princeton NJ 08540

US License No. 2003

at: (if you wish to list the drug product facility)

BLA 125553
Page 4

GP Grenzach Produktions GmbH
Grenzach-Wylen, Germany

Product of xxxx (Consider adding the country of origin for your product per U.S. Customs Border and Protection 19 CFR 134.11)

7. Add the statement "No preservative."
8. Delete the statement [REDACTED] (b) (4) from the bottom panel.
9. Add the statement "Do Not Freeze. Do Not Shake" with the storage and handling information on the bottom panel.
10. Delete the statement [REDACTED] (b) (4) This information should appear in the Prescribing Information in section 2 – Dosage and Administration along with the preparation instructions per 21 CFR 201.57(c)(3).
11. Add the amounts of inactive ingredients to comply with 21 CFR 201.100(b)(iii) and USP Official 12/1/2014 –4/30/2015, USP 37/NF 32, <1091> Labeling of Inactive Ingredients, by listing the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). For example, revise "Each prefilled syringe contains 480 micrograms filgrastim-bflm in 0.8 mL (600 mcg/mL). Inactive ingredients: glutamic acid... and sorbitol (E420)" to read as:

Each 0.8 mL prefilled syringe contains 480 mcg filgrastim-bflm, glutamic acid (1.178 mg), polysorbate 80 (0.032 mg), sorbitol (40 mg), and water for injection. Sodium hydroxide may be added to adjust pH.

Note deletion of [REDACTED] (b) (4)

12. Add the statement "A recombinant Granulocyte Colony-Stimulating Factor (rG-CSF) derived from *E Coli*." to comply with per 21 CFR 610.61(q).

E. Carton Labeling 1-Pack of 300 mcg and 480 mcg strengths

1. Relocate the NDC from the side panels to the top of the PDP per 21 CFR 201.2.
2. See comments D1, D2, D3, D5, D6, D7, D8, D9, D10, D11, and D12.

F. Blister Foil Labeling 300 mcg and 480 mcg strengths

1. Relocate the statement "Single-Use Only" to appear under the route of administration statement.

BLA 125553
Page 5

2. See comments D1 and D7.
3. Add the statements "Do Not Freeze. Do Not Shake." with the storage and handling information.
4. Revise manufacturing information to comply with per 21 CFR 600.3(t), 21 CFR 610.61(b). For example:

"Manufacturer:" or "Manufactured by:" (Licensee or Applicant on the 356h form)
Sandoz
Princeton NJ 08540
US License No. 2003

G. Syringe Label for 300 mcg and 480 mcg strengths

1. We consider the PFS Container Label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.
2. Consider deleting (b) (4)
3. Revise **▲ SANDOZ** to appear as Sandoz US Lic. No 2003.
4. Delete the abbreviations "SC/IV" that appear in red font. Consider expanding the abbreviation to read "Subcutaneous or Intravenous Use" and relocating under the dosage form statement (see comment G.2.) or strength statement to reduce the likelihood of confusing the abbreviations for other terms as discussed by ISMP.¹ This can be achieved by reducing the prominence of the manufacturer information as in comment G.3.
5. Remove the volume statements (b) (4) on the right side of the label as this information is redundant and occupies space.

We have the following comments regarding your proposed labeling (prescribing information) submitted on January 22, 2015.

¹ ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 September 8]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>

BLA 125553
Page 6

H. Please see the attached recently approved labeling for US-licensed Neupogen in PLR format, available at Drugs@FDA. We recommend that you incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications, in your draft proposed labeling. You may use this PLR format labeling as a template to facilitate a consistent approach to your draft proposed PLR format labeling. Submit to your BLA annotated labeling that describes the areas where your proposed labeling differs from the approved Neupogen labeling. Please also submit your proposed labeling in tracked changes where the areas that differ are noted.

Please respond via email by 12:00 PM ET, February 11, 2015.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachment:
US-licensed Neupogen labeling in PLR format, available at Drugs@FDA

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
02/06/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, February 04, 2015 12:56 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: DMEPA Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Feb 5

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[DMEPA Information Request:](#)

Please provide your response to me by email by **1:00 PM ET, February 5, 2015.**

1. The information you have provided in January 22, 2015 submission did not address Question 4 from Agency's Information Request sent to you on January 9, 2015. As a result, we reiterate the request: For the 8 patients that were unable to set at least one of the doses within acceptable tolerance, please provide information on what doses those participants prepared/dialed. Otherwise, state that you did not collect that data.
2. For the product marketed in Europe as Zarzio, please provide the following information:
 - a. It appears that Zarzio is marketed in Europe in a syringe with an active needle guard and a syringe without needle guard. Please provide information describing the design of both prefilled syringes, and if possible images that display the actual syringes. Also, comment on why two syringe designs are marketed in Europe when you have sought a single syringe design in the US.
 - b. Please state whether the syringe with an active needle guard used for Zarzio in Europe is the same syringe design, including the same needle guard, proposed to be marketed in US.
 - c. Please describe whether you have had any reports of medication errors, specifically dosing errors reported with partial dosing for the Zarzio product in Europe. In providing this information, if possible, please identify the type of syringe presentation associated with the report.
3. Please state whether you aware of any other products that are marketed (in the US or outside the US) in the same syringe presentation, with the same active needle guard, that you propose to market your proposed product in the United States.
4. Please provide ten (10) syringes of each strength, bearing your updated labeling, for our review.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/04/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, February 03, 2015 1:17 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Feb 5

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

CMC Information Request:

Please provide your response to me by email by **12:00 PM ET, February 5, 2015.**

1. Your proposed release and stability specification for extractable volume of EP2006 drug product (DP) is “not less than (b) (4)” (300 mcg/0.5 mL strength) and “not less than (b) (4)” (480 mcg/0.8 mL strength). The proposed acceptance criteria would result in (b) (4) lower total amount of product for the 300 mcg/0.5 mL strength and (b) (4) lower total amount of product for the 480 mcg/0.8 mL strength. The amount of product could be even lower if the protein concentration of the EP2006 DP is at the lower end of the specification. Revise your acceptance criteria to ensure that your drug product will deliver the stated amount of “not less than (b) (4)” (300 mcg/0.5 mL strength) and not less than (b) (4) (480 mcg/0.8 mL strength).
2. Your proposed acceptance criteria for sum of impurities by RP-HPLC are (b) (4) for release and stability of EP2006 DP, respectively. Historical data of EP2006 DP provided in the submission show that sum of impurities of EP2006 DP are 0.9-2.4% at release and 3.4-5.3% at stability (36 months). These data include clinical EP2006 DP and process validation EP2006 DP batches. We are concerned that your current acceptance criterion for sum of impurities at release of (b) (4) can lead you to fail a stability specification for sum of impurities. Based on the stability data of EP2006 DP process validation batches, the sum of impurities can increase up to 2.7 % by the 24 month time point. This means that the sum of impurities of EP2006 DP lots released with a sum of impurities result of (b) (4) will likely result in an out of specification. In addition, your analysis of US-licensed Neupogen by RP-HPLC indicates that the sum of impurities in the reference product is 3.5-5.9% for lots of different shelf life collected from the market. (b) (4)
(b) (4) Revise your acceptance criteria for sum of impurities determined by RP-HPLC taking into consideration your analysis of US-licensed Neupogen and your clinical and manufacturing experience with EP2006 DP.
3. Your justification for maintaining the (b) (4) as criterion for assignment of equipotency of in house primary and secondary reference materials considering standard error of the last four reference materials is not appropriate because the variability is enhanced. You should establish acceptance criteria for assignment of equipotency from testing a single primary reference standard that has been calibrated using an international reference standard for GCSF. Revise your criterion for assignment of equipotency to be more stringent (b) (4). The variability of the biological activity data may be controlled, for example, by increasing the number of replicates in the bioassay conducted to qualify the reference standard.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
02/03/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, January 27, 2015 6:29 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 28

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

CMC Information Request:

Please provide your response to me by email by **4:00 PM ET, January 28, 2015.**

You provided a post-approval stability protocol for EP2006 drug product (DP) in section 3.2.P.8.2 and in a document entitled “3.2.R Shelf life extension protocol” proposed to extend the shelf life of EP2006 DP to 36 months. There is a discrepancy in the analytical testing proposed in section 3.2.P.8.2 (Table 1-2) and in document “3.2.R Shelf life extension protocol” (Table 5-2). Additionally, we note these protocols skip testing for appearance, clarity, extractable volume, IEF and particulate matter at specific testing points. We are concerned that your proposed stability testing protocol is not adequate to ensure that the product will maintain its purity, potency and safety over the proposed shelf life. To address our concern provide the following:

1. Clarify which proposed stability protocol (Table 1-2 in section 3.2.P.8.2, or Table 5-2 in document “3.2.R Shelf life extension protocol”) will be used in the stability commitment and for extension of the shelf life of EP2006 DP, and update the two sections of the BLA to be consistent.
2. Revise your post-approval stability protocol to be consistent with the revised shelf life specifications (e.g. inclusion of potency testing). Additionally, revise your protocol to test quality attributes such as appearance, clarity, and particulate matter at all testing points. Extractable volume and IEF testing may be conducted less frequently (b) (4).

Please respond to me via email and officially submit your response to the BLA **by January 30, 2015.**

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)

FDA/CDER/OND/OHOP

(301) 796-5357 (phone)

(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/30/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125553

GENERAL ADVICE

Sandoz, Inc.
506 Carnegie Center Drive
Suite 400
Princeton, NJ 08540

ATTENTION: John Pakulski, RPh.
Head, US Biopharmaceutical Regulatory Affairs

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for EP2006.

On January 20, 2015, at 11:09 am, an information request intended for you was inadvertently emailed to a U.S. Agent not associated with Sandoz. The information request was subsequently emailed to you on January 20, 2015, at 2:38 pm.

On January 20, 2015, at 11:14 am, the recipient of the information notified us that he had received the email in error. The recipient agreed to delete the email. The recipient further agreed not to retain any copies of the information or to use, distribute, or disclose the email or the contents thereof. On January 20, 2015, the Office of New Drugs (OND) sent a letter to the recipient, requesting that he provide OND with a letter 1) confirming this agreement, and 2) indicating that he has deleted the email and any copies. OND also informed the recipient that we would be notifying you of the inadvertent disclosure of this information.

We apologize for the inadvertent disclosure of your information. CDER takes its disclosure responsibilities very seriously and we make every effort to ensure that information is disclosed only in accordance with applicable laws and regulations.

If you have any questions, please call me at 301-796-0869.

Sincerely,

Leah Christl, Ph.D.
Associate Director for Therapeutic Biologics
Therapeutic Biologics and Biosimilars Team
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH A CHRISTL
01/29/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, January 21, 2015 3:55 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 27

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and officially submit your response to the BLA.

CMC Information Request:

Please provide your response to me by email by **4:00 PM ET, January 27, 2015.**

1. You did not provide leachable and extractable data for the drug substance (DS) container closure system. To address this deficiency provide the following:
 - a. Extractable and leachable data from the container closure system and leachables data from the EP2006 DS process using suitable methods. Analysis of extractables and leachables should include evaluation of organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semivolatile (e.g., GC-MS) species, and metals (e.g., ICP-MS) (refer to Markovic, I. Evaluation of safety and quality impact of extractable and leachable substances in therapeutic biologic protein products: a risk-based perspective. Expert Opin. Drug Saf. (2007) 6(5)). The extractable and leachable assessment should include their chemical identification and quantification.
 - b. Risk assessment of extractables and leachables identified in your proposed container closure system for EP2006 DS and leachables from the EP2006 DS process. You may consider the extractable data conducted by the manufacturers of the components of the container closure system and the materials used in the manufacture of EP2006 DS (b) (4) to conduct an initial risk assessment of potential extractables and leachables.

Additional information regarding extractables and leachables should be provided per *FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999)*.

2. Revise your release and stability specifications for drug substance (DS) and drug product (DP) to address the following:

- a. Establish objective and quantitative (when possible) acceptance criteria for identity methods (molecular size, hydrophobicity and isoelectric point). Acceptance criteria such as “correspond to reference” are not appropriate.
 - b. Provide method validation and transfer reports (if applicable) for the peptide mapping method intended to be included as orthogonal identity tests in the DS release specifications.
 - c. Process-related impurities such as E. coli host cell proteins and residual DNA are not expected to change during storage. Consider removing these tests from the stability specifications of EP2006 DS.
 - d. Your release and stability specification for extractable volume of EP2006 DP is “not less of (b) (4) (300 mcg/0.5 ml strength) and “not less than (b) (4) (480 mcg/0.8 ml strength). Revise your acceptance criterion for extractable volume to include two significant figures. In addition, specify the rounding procedures applied to extractable data.
 - e. Describe your control strategy for the levels of sub-visible particles (b) (4) in the EP2006 DP.
 - f. You proposed to revise the acceptance criterion for pH of the EP2006 DP as (b) (4) based on manufacturing experience of lots of EP2006 DP manufactured for the US market and for other markets. The data provided in Table 7-1 of the response to information request (question 1) dated January 14, 2015 indicate that your process is able produce EP2006 DP with pH in the range of (b) (4). Revise the upper limit of the acceptance criterion to better reflect manufacturing experience of the EP2006 DP for the US market.
 - g. You proposed to introduce the relative retention time (0.8-0.9 min.) and relative peak heights (60-140%) of two EP2006 peptide peaks (G4, G12) as acceptance criterion for the peptide mapping method used as orthogonal identity test in the release specification of EP2006 DS. Your peptide map method has at least 12 well resolved peptide peaks. Additionally, based on the peptide map method data provided, it appears that your method is also quite reproducible. Revise your acceptance criterion for peptide mapping to include all major EP2006 peptide peaks to account for the complete sequence of the EP2006 protein.
3. You control the concentration of the excipients in the final EP2006 drug product in (b) (4) steps: (b) (4)
- (b) (4)
- You should establish a more appropriate control strategy for the concentration of excipients in the final EP2006 DP. Establish a control strategy for the excipients of the final EP2006 DP that includes (b) (4)
- (b) (4)
4. The reference standards or materials section and the response to IR dated October 10, 2014 describe the procedures to declare the biological activity of EP2006 in-house primary and secondary reference materials. In the response to the above referred IR you state the following regarding the evaluation of the in vitro assay used to declare the potency of the EP2006 in-house reference materials:
- “The in-vitro assay is evaluated as follows: If the mean relative potency of the new EP2006 in house primary reference material is between (b) (4) of the used reference material, the new reference material will be assigned as having 100% potency, corresponding to 100% of the biological activity of the previous

reference material (U/mg EP2006). If the mean relative potency of the new in-house primary reference material is outside this range, a correction factor may be introduced”.

The range of (b) (4) proposed for declaration of 100% potency of your EP2006 in-house primary and secondary reference materials is too wide. Revise your proposed range to be more stringent (b) (4). The variability of the biological activity data may be controlled by, for example, by increasing the number of replicates in the bioassay conducted to qualify the reference standard.

Additionally, clarify whether the EP2006 in-house primary reference material will be calibrated against an international reference standard for GCSF and provide information about the procedures for declaration of potency of the EP2006 in house primary reference material.

5. The method validation report for host cell proteins (b) (4) entitled “Validation of the Sandwich ELISA to Determine the Concentration of Host Cell Proteins (HCP) in EP2006 test Items” states that “the reference item of this study was (b) (4). The IgG antibodies used were affinity purified (b) (4). (b) (4). Provide information regarding the source of (b) (4) antibodies used in the HCP ELISA assay.

6. Provide expansions of the ^1H - ^{15}N HSQC spectra of EP2006, US-licensed Neupogen and EU-approved Neupogen (Figures 5-14 through 5-21, section 3.2.S.3.1). The expansions may be provided by quadrant (e.g. 4 quadrants per spectrum). In addition, please draw the cross-peaks in the overlaid spectra in different color and “transparent” so the cross-peaks of each product can be easily distinguished.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/21/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, January 20, 2015 2:38 PM
To: Pakulski, John
Cc: Liu, Zhengyu; Boehmer, Jessica
Subject: Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 21

Importance: High

Follow Up Flag: Follow up
Flag Status: Completed

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request below. Please respond to me via email and officially submit your response to the BLA.

BMAB Information Request:

Please provide your response to me by email by **4:00 PM ET, tomorrow, January 21, 2015.**

With regard to the [redacted] hold times, please clarify if you intend to hold [redacted] for the durations specified in Table 4-9 in Section 3.2.S.2.2 [redacted]. If so, update the hold time validation protocol to include the validation of hold times at [redacted] (b) (4) Provide the updated protocol. Alternatively, you may limit the hold times at [redacted] for [redacted] (b) (4) and update the BLA accordingly.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/20/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, January 13, 2015 5:26 PM
To: Pakulski, John
Cc: Boehmer, Jessica; Liu, Zhengyu
Subject: CMC/Micro Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 21

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request below. Please respond to me via email and then officially submit your response to the BLA.

[CMC Micro Information Request:](#)

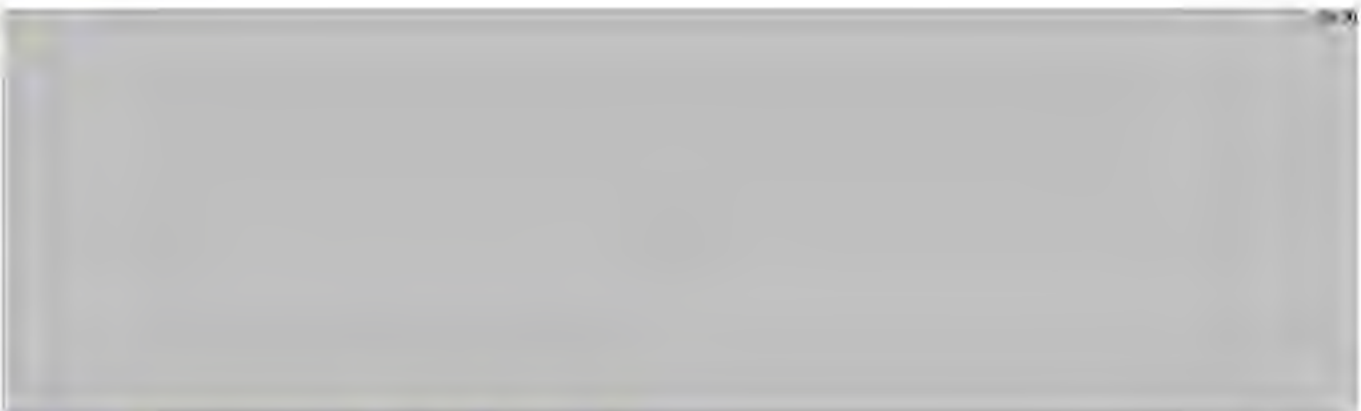
Please provide your response to me by email by **2:00 PM ET, January 21, 2015.**

- 1) The SDN 14 (eCTD sequence 0013) response to Question 3c stated that the method sensitivity for the dye ingress test method was determined to be 25 μ m based on studies conducted with vials. Clarify how this value was determined.

2)



3)



- 4) The SDN 14 response to Question 10b states that



5) Regarding the 2010 – 2013 (b) (4) validation data presented in the SDN 14 response to Question 11b:

a) Table 11-3 of the response describes (b) (4) whereas Table 5-4 of Module 3.2.P.3.5.5.7.2 describes (b) (4). Clarify how the validation (b) (4) presented in Table 11-3 correlate with those presented in Table 5-4.

b) Clarify why an Fo acceptance criterion of (b) (4) was used for the initial 2010 validation studies, whereas a criterion of (b) (4) was used for the 2011, 2012 and 2013 requalification studies.

6) Regarding media fill validation:

a) Module 3.2.P.3.5.6.2 states that (b) (4) whereas footnote 2 of Module Table 6-1 indicates that a (b) (4) that (b) (4). Clarify what occurred (b) (4).

b) Tables 6-2 and 6-4 indicate that the (b) (4). Clarify how these deviations impacted evaluation of the media fill results.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/13/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: December 3, 2014

Application Number: BLA 125553/0

Product Name: EP2006, Proposed Biosimilar to US-licensed Neupogen

Sponsor/Applicant Name: Sandoz, Inc.

Subject: Immunogenicity testing results

FDA Participants

Division of Hematology Products

Albert Deisseroth, MD, PhD, Cross-Discipline Team Leader
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Biotechnology Products (OBP)/Division of Therapeutic Proteins

Susan Kirshner, PhD, Review Chief
Frederick Mills, PhD, Biologist
Faruk Sheikh, PhD, Staff Fellow

OND Therapeutic Biologics and Biosimilars Team

Carla Lankford, MD, PhD, Science Policy Analyst

Sponsor/Applicant Participants

Catherine Cornu-Artis – Head Global Clinical Development
Ingrid Schwarzenberger – Head Global Regulatory Affairs
Joerg Windisch – Chief Scientific Officer
Gregor Schaffar - Head Clinical Bioanalytics
Sigrid Balser - Head Biostatistics & Clinical Submission
Stefan Kramer – Global Program Leader
Hannes Wallnoefer – Global Regulatory Manager
Zhengyu (Eddy) Liu – US Manager Regulatory Affairs
John Pakulski – Head US Regulatory Affairs

1.0 BACKGROUND:

FDA requested the teleconference with Sandoz to discuss their immunogenicity testing results. Specifically, FDA wanted to discuss:

- a) Additional testing of samples
- b) Obtaining patient data from the 301 and 302 studies.

2.0 DISCUSSION:

Sandoz indicated they have reanalyzed the study 302 data using a reset cut-point; in addition, Sandoz will test all positive samples with a confirmatory assay. Any sample that is confirmed positive will be tested with a neutralizing antibody assay. The Agency indicated the proposed plan is acceptable.

Sandoz indicated they will send the missing Excel data files that should have been included with their November 17, 2014 response to FDA's Immunogenicity information request.

3.0 ACTION ITEMS:

Sandoz will send the missing Excel data sheets.

Sandoz will send the new immunogenicity data by December 24, 2014.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/13/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, January 13, 2015 11:24 AM
To: Pakulski, John
Cc: Boehmer, Jessica; Liu, Zhengyu
Subject: Statistics Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 14th

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

Statistical Information Request:

Please provide your response to me by email by **3:00 PM ET, tomorrow, January 14, 2015.**

- 1) Please send an executable SAS program, as simple as possible, so that we can understand and recreate your ANC profile graph. When data sets are called in the SAS program, identify them by name and date submitted to the BLA.
- 2) Please clarify why the sample sizes on day 2 are larger than the sample sizes on day 1.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/13/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, January 09, 2015 4:42 PM
To: Pakulski, John
Cc: Boehmer, Jessica; Liu, Zhengyu
Subject: DMEPA Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 13th

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[DMEPA Information Request:](#)

Please provide your response to me by email by **3:00 PM ET, January 13, 2015.**

We are reviewing your Human Factors study results and need the following information:

1. If available, please provide your full Human Factors Study Results report. If unable to provide the full report, at a minimum please provide information from Comments 2 through 5 from this Information Request.
2. Please provide Failure Modes and Effects Analysis Evaluation/Risk Analysis Evaluation
3. For the 11 patients that were able to set correct doses each time, please provide information regarding which ones were caregivers and which ones were patients.
4. For the 9 patients that were unable to set at least one of the doses within acceptable tolerance, please provide information what doses those participants prepared/dialed.
5. If you collected subjective responses from participants regarding their preparation of the product, please submit that information as well. It is unclear from your submission dated December 2, 2014 whether the 0.1 mL and 0.2 mL markings are visible on the 0.8 mL syringe, or whether the spring of the needle interferes with readability of 0.1 mL and 0.2 mL markings on both syringes. Please provide information to clarify.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/09/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, January 06, 2015 3:29 PM
To: Liu, Zhengyu; Pakulski, John
Cc: Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 13th

Importance: High

Dear John and Eddy,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request below. Please respond to me via email and then officially submit your response to the BLA.

CMC Information Request:

Please provide your response to me by email by **2:00 PM ET, January 13, 2015**.

- The proposed bioburden [REDACTED] and endotoxin [REDACTED] limits for [REDACTED] are alert limits. Please commit as a post-market commitment to update the BLA with bioburden and endotoxin action limits for [REDACTED] in an Annual Report when data from more EP2006 batches are available. Tighten the endotoxin limit [REDACTED].
- You indicate in Table 0-3, "Overview of changes introduced to the BLA application STN125553/0" in amendment dated 11/12/2014 (Sequence 19) that
[REDACTED]

Update the BLA with the correct information.
- Provide the protocol for validation of [REDACTED] hold times at scale from microbiology perspective. Please note that the bioburden and endotoxin level [REDACTED] should not increase during the hold time.
- You committed in an amendment dated 8/22/2014 (sequence 10) to update the bioburden specification of the [REDACTED]. The specification is still not updated. Please update the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
01/06/2015

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Saturday, December 27, 2014 8:56 PM
To: john.pakulski@sandoz.com; zhengyu.liu@sandoz.com
Cc: Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 5th and 12th

Importance: High

Dear John and Eddy,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

CMC Information Request:

Please provide your response to me by email by **2:00 PM ET, January 5, 2015. Responses to Items 2 and 7 may be provided by January 12, 2015.**

1. Revise your release and stability specifications for EP2006 drug substance (DS) and EP2006 drug product (DP) to address the following:
 - a. You did not include a specification for potency in your proposed release and stability program for EP2006 DP. Establish release and stability specifications for potency for EP2006 drug product.
 - b. You propose SE-HPLC, RP-HPLC, and IEF as orthogonal identity tests. These tests are not sufficient to confirm the identity of EP2006 because they do not assess a unique characteristic of your product. In addition, EP2006 DP is manufactured at a CMO (GP Grenzach Produktions GmbH (GPG), Germany) where other products may also be manufactured. Thus, an identity test that unequivocally distinguishes EP2006 from other products manufactured at the facility is critical. Include an identity test that evaluates a unique characteristic of your product, such as peptide mapping, in the release specifications of EP2006 DS and DP. Your specifications for identity should include quantitative (when possible) and objective acceptance criteria. An acceptance criterion such as “correspond to reference” is not appropriate.
 - c. Your specifications for purity by RP-HPLC for release and stability of EP2006 DS and DP include acceptance criteria for sum of impurities (%) and largest individual impurity (%). Based on your characterization studies, the RP-HPLC method evaluates product-related substances and impurities including oxidized and deamidated EP2006 species as well as nor-leucine EP2006 variants. Because the impact of these species on safety and efficacy may be different (b) (4), you should establish acceptance criteria for individual species. Please revise your acceptance criteria for release and stability of EP2006 DS and DP to include acceptance criteria for the individual species evaluated by the RP-HPLC method. The acceptance criteria should consider

the impact of the individual species on safety and efficacy, the results of your analysis of the reference product, US-licensed Neupogen, and your manufacturing experience with EP2006 DS and DP.

- d. Your release and stability specification for bioactivity for EP2006 DS is (b) (4). Revise your acceptance criterion for bioactivity to include (b) (4). In addition, specify the rounding procedures applied to the bioactivity data.
 - e. The methods to assess purity included in your release and stability specifications for EP2006 DS and DP are not suitable to evaluate (b) (4) EP2006 species. Include SDS-PAGE as an orthogonal method for purity in the release and stability specifications of EP2006 DS and DP to evaluate (b) (4) EP2006 species that can be unnoticed by SEC and to monitor other process- and product-related impurities.
 - f. Your stability acceptance criterion of (b) (4) by IEF, for EP2006 DP does not reflect the results of the analytical testing you conducted on the reference product, US-licensed Neupogen, or your clinical and manufacturing experience with EP2006 DP. Based on your results, there are (b) (4) with intensity of (b) (4) in US-licensed Neupogen lots collected from the market (different shelf lives). The number of bands with intensity of (b) (4) in the release and stability results of EP2006 DP was (b) (4), respectively. Revise the acceptance criterion for stability of EP2006 DP taking into consideration the results of your analysis of US-licensed Neupogen and your clinical and manufacturing experience with EP2006 DP.
 - g. The proposed acceptance criterion for EP2006 DS and DP pH is (b) (4). The proposed upper limit is not supported by your clinical and manufacturing experience, where the maximum measurement for the upper limit was to (b) (4). Please revise the upper limit of the acceptance criterion for pH for both EP2006 DS and DP.
2. You provided in-use stability data (“*Compatibility of EP2006 DP with solutions containing glucose and HSA; stability in various container materials*”) of EP2006 DP and EU-approved Neupogen in 5% glucose in containers of different materials. Content, by RP-HPLC, was the only quality attribute evaluated. Your in-use stability studies did not include evaluation of potency, purity, aggregates, and particulates. Provide the in-use stability data of EP2006 in 5% glucose and 2 mg/ml HSA that includes evaluation of potency, purity, aggregates, and particulates. We recommend that you conduct your in-use stability study using dilution conditions (e.g., concentration of GCSF and HSA) similar to those described in the US-licensed Neupogen labeling.
 3. Your characterization studies of EP2006 include characterization of EP2006 product-related substances and EP2006 product-related impurities. Please specify which EP2006 species are product-related substances and which are product-related impurities.
 4. You provided a summary of the manufacturing process validation exercise for EP2006 DP and reported the results of in-process and release control tests as well as additional testing on (b) (4) to support process validation and hold times. However, you did not provide the process parameters used to control the manufacturing process. Provide information and justify the process parameters and operating

ranges [REDACTED] used to manufacture each of the EP2006 DP process validation batches. In addition, provide the process validation protocol executed in the EP2006 DP process validation exercise.

5. You provided data from a retrospective shipping validation study to support shipping of EP2006 DP from its [REDACTED]

[REDACTED] Update your drug product shipping procedure to specify an upper limit for the temperature during shipping and provide a justification for the proposed temperature upper limit. In addition, provide qualification data for the containers used to ship EP2006 DP.

6. In addition to a retrospective shipping validation study, you proposed a prospective shipping validation study [REDACTED]

[REDACTED] Please provide your protocol for the prospective shipping validation study of EP2006 DP that you plan to execute.

7. You evaluated extractables and leachables from the container closure system, and leachable from the EP2006 DP manufacturing process, by the routine RP-HPLC purity method used for release and stability testing of EP2006 DP. Your RP-HPLC method does not appear to be suitable for evaluation of all types of extractables and leachables in your product. Analysis of extractables and leachables should include evaluation of organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species, and metals (e.g., ICP-MS) (*Markovic, I. Evaluation of safety and quality impact of extractable and leachable substances in therapeutic biologic protein products: a risk-based perspective. Expert Opin. Drug Saf. (2007) 6(5)*). The extractable and leachable assessment should include their chemical identification and quantification. To address this deficiency provide the following:

- Extractable and leachable data from the container closure system and leachables data from the EP2006 DP process using suitable methods.
- Risk assessment of extractables and leachables identified in your proposed container closure system for EP2006 DP and leachables from the EP2006 DP process. You may consider the extractable data conducted by the manufacturers of the components of the container closure system and the materials used in the manufacture of EP2006 DP [REDACTED] to conduct an initial risk assessment of potential extractables and leachables.
- Since the presence of [REDACTED] in syringes can impact product quality and stability, we recommend that you evaluate and control the levels of [REDACTED] in your pre-filled syringes and provide a risk assessment for the impact of [REDACTED] on the quality, stability and safety of your drug product.
- Provide information on the strategy to control the levels of [REDACTED] leached into your product from the container closure system.

Additional information regarding extractables and leachables should be provided per *FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999)*.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
12/27/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, December 16, 2014 4:50 PM
To: john.pakulski@sandoz.com
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due December 19th

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[Clinical Information Request:](#)

Please provide your response to me by email by **2:00 PM ET, December 19, 2014.**

You have stated that the needle safety device (NSD) utilized for your product is the UltraSafe Passive Needle Guard (b) (4), manufactured by (b) (4) and cleared in CDRH under (b) (4). Within the 510(k) process, a manufacturer may be able to make changes to a device while only documenting the changes internally. Your submission does not contain information related to a change control process as it relates to the use of the aforementioned 510(k) device. Please provide the change control procedures that are in place that will ensure continued compatibility of your product with the UltraSafe passive Needle Guard (b) (4).

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
12/16/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, December 11, 2014 5:10 PM
To: john.pakulski@sandoz.com
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due December 15th

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

Clinical Information Request:

Please provide your response to me by email by **4:00 PM, December 15, 2014.**

1. Regarding about SN0020 submitted 12/2/2014:

a) On Annex 5, you cite the following human factors study:

EP2006_PFS_30_48_in (b) (4) system, Training Definition Study Report 8116 0016a WIP01, 12th March 2014

The citation is not hyperlinked. Please identify where in the BLA this study can be found. If it is not in the BLA, please submit the full study report.

b) In item #7 of the cover letter, you indicate that you are submitting corrected datasets for EP06-101, EP06-102, EP06-104, EP06-105, and EP06-301. Please describe the actual corrections made for each of the data sets. Are the corrections to variable names (if so, which variable names were changed), data elements (under which variables), etc?

2. During the review of records at Sandoz Pharmaceuticals in Holzkirchen, Germany, November 17-21, 2014, the FDA Inspector determined that subject 703-07 in Protocol EP06-302 received commercial filgrastim rather than study drug in Cycle 2. This subject was not identified as having received commercial filgrastim in your prior revised ex.xpt file. Please clarify if this new major protocol deviation will alter the results of any of the efficacy analyses in your study report for Protocol EP06-302.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
12/11/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, November 18, 2014 3:37 PM
To: john.pakulski@sandoz.com
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 21

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email **by 2:00 PM November 21, 2014**, and then officially submit your response to the BLA.

CMC Information Request:

1. Please provide the following information about the EP2006, US-licensed Neupogen and EU-approved Neupogen batches (unless otherwise specified) used in clinical studies EP06-101, EP06-102, EP06-103, EP06-105, EP06-109, EP06-301 and EP06-302:
 - a. Content
 - b. Bioactivity
 - c. Expiry (US-licensed Neupogen and EU-approved Neupogen) and manufacturing date (EP2006)

Provide the data using the same units (e.g. percentage of bioactivity) for all the three products.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
11/18/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, November 18, 2014 1:23 PM
To: john.pakulski@sandoz.com
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: FDA Advice re: July 1 submission - HF study - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen

Importance: High

Dear John,

Please reference BLA 125553 for EP2006.

[DMEPA Advice:](#)

With reference to your July 1, 2014, submission of data from Novartis' Human Factors study for its proposed secukinumab injection, we do not agree that this data can be extrapolated to EP2006 due to multiple differences between the two products (i.e., indication, dose, patient population, and training) that ultimately may affect the applicability of the results of the Human Factors study. However, EP2006 is proposed to be marketed in a similarly designed prefilled syringe that is currently marketed for Neupogen. Since the Neupogen prefilled syringe is used in a similar manner in the same patient population without any concerning trends in reported use errors, we do not think a Human Factors study for EP2006 is needed.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
11/18/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 13, 2014

Application Number: BLA 125553

Product Name: EP2006, Proposed Biosimilar to Neupogen

Sponsor/Applicant Name: Sandoz, Inc.

Subject: OSI/ORA Holzkirchen inspection

FDA Participants

Office of Scientific Investigations

William H. Taylor, PhD, DABT, CAPT, U.S. Public Health Service, Director, Division of Bioequivalence and Good Laboratory Practice Compliance
Nicola Fenty-Stewart, PhD, Project Manager

Division of Hematology Products

Jessica Boehmer, MBA, Regulatory Project Manager

Sponsor/Applicant Participants

Sandoz Inc.

John M. Pakulski, RPh, Head, U.S. Biopharmaceutical Regulatory Affairs

1.0 BACKGROUND:

OSI/ORA is conducting inspections at the site in Holzkirchen, Germany. According to the June 18, 2014 amendment to BLA 125553, records should be located at this site and OSI/ORA planned their inspections accordingly. Sandoz indicated the requested documents for EP06 103 are at the Cologne site and that they were not willing to send source documents from the Cologne site.

ORA is awaiting documents from the EP06 109 and EP06 101 studies that will be shipped to Holzkirchen.

2.0 DISCUSSION:

FDA requested that the Applicant ship the requested records to the Holzkirchen, Germany site, as the June 18, 2014 amendment to BLA 125553 indicated this is where the records would be located.

FDA noted that failure to comply with this request could have significant implications to review of the application.

Sandoz indicated that they would provide an update by the end of the day, November 13, 2014.

3.0 ACTION ITEMS:

Sandoz will update the Agency regarding the requested records and if/when they will be shipped and available for review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
11/13/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, November 12, 2014 3:53 PM
To: Pakulski, John
Cc: Boehmer, Jessica
Subject: RE: BLA 125553 EP2006 - Response timing for CMC Information Requests dated Nov 7 and Oct 31

Importance: High

Dear John,

Regarding the proposed response timing for the CMC Information Requests:

For November 7 request regarding bioactivity/potency:

1. Please provide your responses for request # 1a and #2 by **2:00 PM, Nov 14 2014**
2. Please provide your responses for request # 1b by **12:00 PM, Nov 17 2014**

For October 31 request regarding content:

Your proposed timeframe for a response in **early December** is acceptable.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

From: Pakulski, John [<mailto:john.pakulski@sandoz.com>]
Sent: Wednesday, November 12, 2014 9:59 AM
To: Boehmer, Jessica
Subject: RE: BLA 125553 EP2006 - Response timing for CMC Information Requests dated Nov 7 and Oct 31

Dear Jessica,

As discussed on phone, please follow-up with the reviewer regarding the November 7 request to confirm that we can provide both data and explanation on November 17th. We cannot provide data today as indicated below.

And we look forward to receiving the feedback on our proposed timing for the October 31 request.

Thanks, John

From: Pakulski, John
Sent: Monday, November 10, 2014 4:31 PM

To: Jessica.Boehmer@fda.hhs.gov

Subject: BLA 125553 EP2006 - Response timing for CMC Information Requests dated Nov 7 and Oct 31

Dear Jessica,

This email concerns the timing of Sandoz' responses to the following CMC Information Requests.

November 7 request regarding bioactivity/potency

We will provide the data as requested on Wednesday, November 12. However, the explanation on the difference between Neupogen PFS and vials will be provided next Tuesday, November 18.

October 31 request regarding content

We plan to provide at the beginning of December. Is this timing OK?

Best regards, John

John M. Pakulski, R.Ph.

Head US Biopharmaceutical Regulatory Affairs

Sandoz Inc., a Novartis company

100 College Road West

Princeton, NJ 08540

USA

Phone: +1 609 627 8861

Cell: (b) (6)

Email: john.pakulski@sandoz.com

Web: <http://www.novartis.com>

Learn more about biosimilars @ www.sandoz-biosimilars.com

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
11/12/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Monday, November 10, 2014 10:52 AM
To: john.pakulski@sandoz.com
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: Immunogenicity Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 17 (#1) and Dec 1 (#2)

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

Immunogenicity Information Request:

1. In your 9th Oct, 2014 correspondence, in response to FDA's concern over the low rate of samples that screened positive for anti-drug antibodies (ADA) in study EP06-302, you provided a summary of the analyses you performed to evaluate the cut-point for the ADA assay. You reported that the lower number of samples screening positive for ADA was considered to be a result of the chemotherapy treatment. However, in study EP06-301, which also evaluated samples from chemotherapy-treated breast cancer patients, 14 of 643 (2.1%) samples screened positive. Therefore, based on the information provided to date, it remains unclear as to whether the assay did not perform as expected when analyzing samples from study EP06-302. In order to further understand the assay performance, FDA has determined that we should perform our own analysis of the primary data from some of your immunogenicity studies. To this end, provide the following information by **3:00 PM ET, November 17, 2014**:
 - a. Primary data generated from studies EP06-109, EP06-301 and EP06-302, including the data for all non-specific binding and negative controls used in the cut-point determination during the study sample analysis. The data should be provided in EXCEL format.
 - b. Details about the equations and the calculation process you used in the determination of cut-point in clinical sample analysis in both facilities.
2. The Neupogen label reports that 11/333 (3%) of cancer patients receiving Neupogen developed anti-Neupogen antibodies. Similarly, literature reports (Laricchia-Robbio et al. J. Cell Physiol 173: 219-226, 1997; Revoltella RP et al. Leukemia and Lymphoma 26: 29-34, 1997) indicate that anti-GCSF antibodies can be found in healthy humans. However, in all your studies, you reported only a single subject who tested positive for anti-GCSF antibodies. Provide your explanation as to why only a single anti-GCSF positive subject was observed in your studies, and provide your assessment of the anti-GCSF antibody prevalence and incidence you expected to observe. The information should be provided by **3:00 PM ET, December 1, 2014**.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
11/10/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, November 07, 2014 9:52 AM
To: john.pakulski@sandoz.com
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: CMC Stats Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 12

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[CMC Statistical Information Request:](#)

Please provide your response by **November 12, 2014**.

1. In your response, dated October 16, 2014, to our request for information, dated October 02, 2014, you provided additional data to support analytical similarity of EP2006 and the reference product, US-licensed Neupogen and to establish an analytical bridge between EP2006, the reference product and EU-approved Neupogen.

Provide the following additional information for the bioactivity potency data present in Table 2-8.

- a. Clarify how many replicates were obtained to calculate the reportable result for each lot.
 - b. For bioactivity data in the table, the five data points of US-licensed Neupogen of Vial are consistently lower than those data from US-licensed Neupogen of PFS. Provide an explanation as to why such difference is observed between the vial and PFS presentations of US-licensed Neupogen. In addition, please submit all available potency data for US-licensed Neupogen for both Vial and PFS presentations.
2. Specify the expiry date for the tested US-licensed Neupogen and EU-approved Neupogen as well as the manufacturing date for the EP2006 in your Table 2-2 for Content and Table 2-8 for Bioactivity. Also specify the testing date for each lot value listed in Table 2-2 and Table 2-8.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)

FDA/CDER/OND/OHOP

(301) 796-5357 (phone)

(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
11/07/2014

Boehmer, Jessica


From: Boehmer, Jessica
Sent: Friday, October 31, 2014 4:40 PM
To: john.pakulski@sandoz.com
Cc: zhengyu.liu@sandoz.com; Boehmer, Jessica
Subject: Clin Pharm Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 5

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[Clinical Pharmacology Information Request:](#)

For studies EP06-109, EP06-101, EP06-103, and EP06-105, complete statistical analyses using the 90% CI,  limits for the single dose ANC and multiple dose CD34+ PD AUEC and Emax parameters. Please submit these results by **Wednesday, November 5, 2014**.

Also, you may submit your response to the Clinical Pharmacology Information Request dated October 29, 2014 on November 5, 2014, as requested.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
10/31/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, October 31, 2014 4:24 PM
To: john.pakulski@sandoz.com
Cc: zhenqyu.liu@sandoz.com; Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request below. Please respond to me via email and then officially submit your response to the BLA.

CMC Information Request:

Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the "strength" of the proposed biosimilar product is the same as that of the reference product. Accordingly, we expect your proposed biosimilar product to have both the same total content of GCSF (in mass or units of activity in a container closure) and the same concentration of GCSF (in mass or units of activity per unit volume) as US-licensed Neupogen (see Q+A I.12 in draft guidance on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009).

You stated that your equivalence testing results for "content" (i.e., concentration as expressed in milligrams per milliliter) of EP2006 in pre-filled syringes (PFS) against US-licensed Neupogen in PFS, and between EP2006 in PFS against the US-licensed Neupogen in both PFS and vials are "inconclusive". In addition, FDA analysis of content of drug product batches manufactured at Lek Pharmaceuticals d.d., Slovenia (LEK), IDT Biologika GmbH, Germany (IDT) and GP Grenzach Produktions GmbH, Germany (GPG) (section 3.2.P.5.4) indicates that the EP2006 drug product validation batches manufactured at GPG (b) (4) (b) (4)

have (b) (4) content compared to EP2006 drug product batches manufactured at IDT ((b) (4)) and LEK ((b) (4)). The (b) (4) content of EP2006 drug product manufactured at GPG appears to be a manufacturing issue. Address the "content" (i.e., concentration as expressed in milligrams per milliliter) of EP2006 drug product manufactured at GPG and submit data to demonstrate that EP2006 drug product manufactured at GPG, the proposed site for your intended commercial product, has the same "strength" as US-licensed Neupogen. (b) (4)

Please provide a time frame for when you plan to provide the requested data.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)

FDA/CDER/OND/OHOP

(301) 796-5357 (phone)

(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
10/31/2014

From: Miller, Mara Bauman
To: [Pakulski, John \(john.pakulski@sandoz.com\)](mailto:John.pakulski@sandoz.com); [Liu, Zhengyu \(zhengyu.liu@sandoz.com\)](mailto:zhengyu.liu@sandoz.com)
Cc: [Boehmer, Jessica](#)
Subject: BLA 125553 for EP2006, Information Request
Date: Wednesday, October 29, 2014 5:56:00 PM
Importance: High

Hello John-

Regarding BLA 125553 for EP2006, we have the following Information Request. Please respond by Monday, November 3, 2014. Provide a response to Jessica Boehmer via email by the due date and then officially submit your response to the BLA.

Regarding the PK substudy within Study EP06-302,

1. Provide summary tables that compare the demographics (e.g., race, age, height, weight, BMI, etc.) and baseline laboratory values of a) the patients included in the two treatments of the PK substudy (EP2006 and Neupogen arms) and b) a comparison of those patients in the PK substudy arms to the overall patients enrolled in those respective treatment arms. Please include the following stratum as an additional factor for these comparisons: adjuvant vs. neoadjuvant.
2. Provide summary tables that compare the actual total dose of each drug administered in Cycle 1 (i.e., chemo, EP2006, and Neupogen) of the patients included in the two treatments of the PK substudy (EP2006 and Neupogen arms).
3. Provide a list of the EP2006 and US licensed Neupogen lots used in the PK substudy.

Thank you,

Mara

Mara Miller, MA
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARA B MILLER
10/29/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, October 16, 2014 4:35 PM
To: Pakulski, John
Cc: Boehmer, Jessica; zhengyu.liu@sandoz.com
Subject: CMC/Micro Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE Jan5

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond by **January 5, 2015**. Please respond to me via email by the due date and then officially submit your response to the BLA.

[CMC/Microbiology Information Request:](#)

Your 09/30/2014 Amendment response to Question 13d (eCTD sequence 0013) only stated theoretical reasons for (b) (4) t. Data from confirmatory validation studies were not provided. Submit data demonstrating that container closure integrity is maintained and (b) (4) is not breached during worst case shipping conditions.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
10/16/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, October 09, 2014 8:44 AM
To: Pakulski, John
Cc: Boehmer, Jessica
Subject: Immunogenicity Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE Oct 21 and Nov 4

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to Item 1 by **October 21, 2014** and to Item 2 by **November 4, 2014**. Please respond to me via email by the due date and then officially submit your response to the BLA.

Immunogenicity Information Request:

Regarding anti-drug antibody binding assay please address the following issues:

1. You submitted results of the immunogenicity screening assay and reported that two of 1583 samples (0.001%) from cancer patients in study EP06-302 screened positive for anti-drug antibodies. FDA recommends a 5% false positive detection incidence for anti-drug antibodies (ADA) screening assays to minimize false negative results (see draft guidance for industry titled "Assay Development for Immunogenicity Testing of Therapeutic Proteins" (2009)). We also note that of 81 samples from study EP06-109 in healthy volunteers 3 samples (3.7%) screened positive. This result is inconsistent with the results obtained in study EP06-302. Overall, we conclude that your screening assay does not perform consistently and that it is not adequate to assess the immunogenicity of EP-2006 or the reference product. Therefore, in light of our concerns regarding your screening assay, the data may not support a demonstration of no clinically meaningful differences between reference product and EP-2006 in terms of the safety, purity, and potency of the product.

To address this deficiency you should provide immunogenicity data for EP2006 and the reference product using a screening assay cutpoint that has a 5% false positive rate and provide evidence that the screening assay is validated. We note that it may be possible to recalculate the cut-point and re-evaluate results from clinical study ADA samples using existing data to begin to address this issue. If recalculation of the cut-point is sufficient to achieve a 5% false positive rate with a validated assay, then additional testing would be necessary to confirm specificity. Any samples that confirm positive should be tested using the neutralizing antibody assay.

Regarding Neutralizing antibody assay:

2. The neutralizing antibody assay cut-point validation results showed considerable variability between analysts. This resulted in your establishing analyst specific cut-points. It is unusual to require analyst specific cut-points for ADA assays. Therefore, our assessment is that your assay was not appropriately optimized and/or that your analysts are not suitably trained. You should revise the assay so that analyst

specific cut-points are unnecessary or explain why your assay provides a meaningful and reliable assessment of neutralizing antibody activity despite the use of analyst specific cut-points.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
10/09/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Monday, October 06, 2014 5:34 PM
To: Pakulski, John
Cc: Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen
DUE Oct 20

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request below. Please respond by **October 20, 2014**. Please respond to me via email by the due date and then officially submit your response to the BLA.

CMC Information Request:

Please establish in-process bioburden and endotoxin limits (b) (4), as committed during the pre-license inspection and update the BLA accordingly.

Please provide a table listing all the in-process bioburden and endotoxin limits for the (b) (4) and update the BLA accordingly. List the bioburden action limits as, (b) (4) and endotoxin action limits as (b) (4).

The endotoxin release data for the (b) (4) provided in Section 3.2.S.4.4, "Batch analyses" are in EU/mL. Please provide endotoxin release data for the (b) (4) in EU/mg and update the BLA accordingly.

The buffer hold time study data obtained from (b) (4) was used to support the hold time validation at scale (b) (4).

(b) (4). Therefore, commit to conduct a hold time study under a QA approved protocol with pre-established bioburden and endotoxin acceptance criteria to demonstrate that (b) (4).

(b) (4) can be held at scale without compromising microbial quality of the process streams. Hold time data should be collected during routine production runs (b) (4). Validation data should be reported in a validation report at the end of the study. Provide the hold time study protocol during the review cycle and provide the projected study completion date. Completion of the study report may be submitted in an Annual Report.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
10/06/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, October 02, 2014 1:07 PM
To: Pakulski, John
Cc: Boehmer, Jessica
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE Oct 16 and 23

Importance: High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to Questions 1 and 10 by **October 16, 2014** and Questions 2 – 9 by **October 23, 2014**. Please respond to me via email by the due date and then officially submit your response to the BLA.

CMC Information Request:

1. You provided data to support analytical similarity between EP2006, US-licensed Neupogen and an EU-approved filgrastim product. The data are derived from two evaluations. Evaluation 1 compared 6 batches of EP2006 drug product (DP), 4 batches of US-licensed Neupogen and 2 batches of the EU-approved filgrastim product. Evaluation 2 compared 6 batches of EP2006 drug substance (DS) and 5 batches of EP2006 DP with 4 batches of the EU-approved filgrastim.

We are reviewing your analytical similarity data (i.e., evaluation 1 and 2) to evaluate whether you have demonstrated that EP2006 is “highly similar” to US-licensed Neupogen and whether you have provided adequate analytical data to scientifically justify the relevance of other comparative data obtained using EU-approved filgrastim to support a demonstration that EP2006 is biosimilar to US-licensed Neupogen.

In your critical quality attribute (CQA) assessment, you identified potency (specific activity in U/mg) and protein concentration (protein content in µg/ml), both with a criticality score of 140, as two of the most critical quality attributes. However, based on the data you submitted, the min-max ranges for potency and protein content of EP2006 appear to be lower than those of US-licensed Neupogen. One possible explanation for these observations may be the limited number of batches of US-licensed Neupogen (4 batches) included in your similarity exercise.

As you have additional US-licensed Neupogen reference lots that were identified during inspection, you should include these lots of US-licensed Neupogen in your similarity exercise. We further recommend that you conduct a statistical analysis of the analytical similarity data, including data from these additional lots, to provide more robust support for your efforts to demonstrate that EP2006 is “highly similar” to the reference product with respect to quality attributes, including but not limited to potency and protein content. We currently recommend that you use a statistical approach to evaluate quality attributes of EP2006 that is consistent with the risk assessment principles set forth in the International Conference on Harmonisation Quality Guidelines Q8, Q9, Q10, and Q11. Consistent with the principles set forth in these guidelines, your program should implement an analytical similarity assessment that is based on a tiered system in which approaches of varying statistical rigor are used. One approach to determining the tier to which a particular quality attribute would be assigned would depend upon a criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity with quality attributes being assigned to tiers commensurate with their risk.

For your program, equivalency testing would be recommended for quality attributes with the highest risk ranking (Tier 1) and generally would include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought. We recommend that you consider the use of quality ranges (mean $\pm X \sigma$, where X should be appropriately justified) for assessing quality attributes with lower risk ranking (Tier 2), and an approach that uses raw data/graphical comparisons for quality attributes with the lowest risk ranking (Tier 3).

In addition to criticality, other factors should be considered in assigning quality attributes and assays to a particular tier using this approach. This approach includes, but it is not limited to, the levels of the attribute in both the reference product and proposed biosimilar product (as determined by your testing), the sensitivity of an assay to detect differences between products, if any, and an understanding of the limitations in the type of statistical analysis that can be performed due to the nature of a quality attribute.

FDA also recommends that you carefully assess your analytical similarity plan to identify and address any other factors that could potentially impact the ability to demonstrate that EP2006 is highly similar to the reference product. This could include, for example, considering the ages of the EP2006 and reference product lots tested, optimizing assays and pre-specifying the criteria under which wider similarity acceptance criteria for a particular assay would be considered appropriate.

We think it would be appropriate for you to consider a statistical approach, such as the one set forth below based on FDA's current thinking on the topic, to evaluate certain quality attributes of the proposed biosimilar and the reference product. You may propose alternative statistical approach(es) to evaluate quality attributes and support a demonstration that EP2006 is highly similar to US-licensed Neupogen.

Further, we note that while a statistical approach to evaluate quality attributes of a proposed biosimilar product may be considered in support of a demonstration that the proposed biosimilar product is highly similar to the reference product, FDA's determination that a proposed biosimilar product is highly similar to the reference product will be based upon the totality of the evidence relevant to the assessment.

A potential approach for the different statistical tiers is described below:

Tier 1 (Equivalence Test): One needs to test against the following null hypothesis.

$H_0: \mu_B - \mu_R \leq -\delta \text{ or } \mu_B - \mu_R \geq \delta$ where μ_B and μ_R are the mean responses of the proposed biosimilar and reference product lots, respectively, and $\delta > 0$ is the equivalence margin.

Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if the $(1-2\alpha)100\%$ two-sided confidence interval of the mean difference is within $(-\delta, \delta)$. In this context, the equivalence margin, δ , would be a function of the variability of the reference product as identified in studies by the biosimilar applicant (σ_R). The equivalence test should be based on the normal distribution, unless the data clearly deviate from the normal distribution.

Tier 2 (Quality Range Approach): The quality range of the reference product for a specific quality attribute is defined as $(\hat{\mu}_R - X\hat{\sigma}_R, \hat{\mu}_R + X\hat{\sigma}_R)$ where the standard deviation multiplier (X) should be appropriately justified.

Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if a sufficient percentage of test lot values (e.g. 90 percent) fall within the quality range.

Please note that each lot contributes one value for each attribute being assessed. Thus, σ_R refers to the standard deviation of those lot values of the reference product.

Ideally, the reference variability, σ_R , should be estimated from testing different lots than those used in statistical equivalence test. This may be a challenge when there are a limited number of lots. The sponsor should provide a plan for how the reference variability, σ_R , will be estimated with a justification for the approach and identify the lots that will be used.

We would also recommend that the same number of replicates be performed within each proposed biosimilar lot as within each reference product lot, and that the same lots be used for equivalence testing, quality range testing, and visual assessment of graphical displays.

Please note that high assay variability would not be a justification for a large σ_R . In such a situation, the assay would need to be optimized and/or the number of replicates increased to reduce variability.

In cases where the equivalence margins or quality ranges are too wide, it may be scientifically justified and appropriate to narrow the margins or range.

One potential statistical approach to evaluate quality attributes is based on a standard statistical test of equivalence with the margin defined as a function of the reference product variability (e.g., $c * \sigma_R$). The constant c would be selected as the value that provides adequate power to show equivalence if there is only a small difference in the true mean between the biosimilar and the reference product, when a moderate number of reference product and biosimilar lots are available for testing. If, for example, we selected $c = 1.5 \sigma_R$ for all sample sizes used in equivalence testing to illustrate this potential statistical approach, the test would yield a positive result if the 90% confidence interval about the difference in sample means lies within $(-1.5 \sigma_R, 1.5 \sigma_R)$. If 10 biosimilar and 10 reference product lots were tested, this would have approximately 84% power of passing equivalence testing when the true underlying mean difference between the proposed biosimilar and reference product lots was equal to $\sigma_R / 8$, assuming a test with $\alpha = 0.05$.

Note that with this potential approach, the margin would be a function of the reference product variability as demonstrated in testing by the biosimilar applicant; therefore, a larger margin would be used for attributes with larger variability. In addition, the confidence level would depend on the number of lots available for testing. For the more limited number of lots described in your briefing package, you may consider calculating the confidence interval with a lower confidence level to ensure adequate power. In this situation, the lower confidence level would be expected to be appropriately addressed by the final manufacturing control strategy. In contrast, when a moderate or greater number of lots are available for testing, the equivalence test would be based on a 90% confidence interval.

2. Provide validation reports for the following methods:

- a. Bioactivity by proliferation with NFS-60 cells
- b. Content and purity by RP-HPLC
- c. Host cell proteins (HCP) by ELISA
- d. Purity by SE-HPLC

3. Your acceptance criterion for identification of various raw materials tested in-house is "complies with test". Revise your specifications for identification of raw materials to specify the method and acceptance criteria applied. Acceptance criteria should be objective and quantitative (e.g. complies with USP <>).

4. You determined that the [REDACTED] used in the manufacture of EP2006 DS is a critical raw material because its quality has the potential to influence the levels of EP2006 norleucine variants. In section 3.2.S.2.6, you indicate that a [REDACTED] was implemented to select lots [REDACTED] of optimal quality. Provide information on the [REDACTED] for [REDACTED] as well as information as to how the specifications for the [REDACTED] (Table 3-20, section 3.2.S.2.3) provide the optimal quality needed to control for EP2006 nor-leucine variants.

5. The proposed action limit for residual [REDACTED] (Table 1-7, section 3.2.S.2.4). This action limit was justified based on a toxicology assessment for levels up to [REDACTED] and the impact [REDACTED] levels have on EP2006 [REDACTED].

The levels of residual [REDACTED] in process validation batches B034028, B034029 and 034030 (Table 1-31, section 3.2.S.2.5) are [REDACTED] which are above the proposed action limit. To address this discrepancy, please provide the following:

- a. Toxicology assessment of [REDACTED]

b. Clarify and justify the proposed in-process control action limit for (b)(4) content

c. A justification as to how the results of residual (b)(4) in the process validation batches demonstrate that the (b)(4) is capable of reducing (b)(4) levels effectively

6. On August 22, 2014, you provided a protocol for validation of (b)(4) lifetime at commercial scale. According to your protocol, the functionality of the (b)(4) is verified by (b)(4)

(b)(4). The parameters to be trended, the testing frequency, and the trending rules that will be applied to monitor (b)(4) performance were not specified. The number of theoretical plates (N), height equivalent of a theoretical plate (HEPT) and symmetry factor were excluded from the protocol. As a result, we find your protocol deficient.

Your protocol should include the following:

a. The parameters to be trended (e.g. purity by RP-HPLC and SE-HPLC, EP2006 content, step yield, residual DNA, HCP), the testing frequency, and the trending rules that will be applied to monitor (b)(4) performance.

b.

c.

7. The process validation (PV) data for the manufacture of EP2006 DS (fermentation, isolation and purification) provided in the 351(k) BLA was generated from (b)(4)

(b)(4) Please update your 351(k) BLA with the (b)(4) PV data. In addition, please confirm whether this process is the proposed commercial manufacturing process for the EP2006 product for which you are requesting licensure by FDA in your 351(k) BLA.

8. Provide the following information regarding all analytical methods used for control of the DS and DP including:
 - a. Date of full validation
 - b. Summary of change history and whether the changes impacted validation status of the analytical method. A justification that the changes did not impact method validation should also be provided.
 - c. The testing sites where each method is executed. Method transfer or re-validation reports (if applicable) should also be provided

Provide this information in tabular format with hyperlinks to module 3.2.R where the method transfer or re-validation reports should be located.

9. Provide information on the qualification of characterization assays used in the analytical similarity exercises including “Method characterization of EP2006 affinity to G-CSF determination by SPR”. Although these documents were provided on inspection, they should be formally submitted to the 351(k) BLA to support that the characterization assays used in the analytical similarity assessment are fit for the intended use.
10. On June 24, 2014, we sent you the following Information Request: “We note that the United States Pharmacopeial Convention recently published a monograph for filgrastim in United States Pharmacopeia 36 -National Formulary 31, Supp. 2 (official 12/1/13). FDA has not yet determined whether the USP monograph for filgrastim is applicable to your proposed biosimilar product. However, we request that you describe whether your proposed biosimilar product meets the standards set forth in the monograph.” Please advise FDA of the date by which you intend to submit a response.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9845 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA L BOEHMER
10/02/2014

BLA 125553 EP2006

- 1) Please submit a Letter of Authorization permitting Agency review of DMF [REDACTED] (b) (4). The DMF referenced [REDACTED] (b) (4) refers to a CBER DMF.
- 2) Regarding the proposed [REDACTED] (b) (4) rubber syringe stoppers:
 - a) The referenced DMF [REDACTED] (b) (4) only provides information regarding the stopper formulation. Submit a Letter of Authorization for the review of DMF [REDACTED] (b) (4) describing validation [REDACTED] (b) (4).
 - b) [REDACTED] (b) (4). Please clarify which configuration is to be used for EP2006 drug product manufacture.
- 3) Regarding validation of container closure integrity of the prefilled syringe system by the microbial and dye ingress methods:
 - a) Submit a description of the positive control used for the microbial ingress test. Include the perforation diameter.
 - b) Submit the method sensitivity limit (minimum detectable perforation diameter) for the microbial ingress test.
 - c) Submit the method sensitivity limit (minimum detectable perforation diameter) for the dye ingress test.
 - d) Submit the detection limit (minimum detectable dye concentration) for the dye ingress test.
- 4) Regarding formulation of bulk EP2006 drug product:
 - a) Specify the established hold times and hold temperatures for the [REDACTED] (b) (4) and excipient [REDACTED] (b) (4).
 - b) Submit microbiology quality data supporting the formulation hold time limit stated in Module 3.2.P.3.5.4.2.2. Readjust the [REDACTED] (b) (4) bioburden limit [REDACTED] (b) (4). It is noted that the limit [REDACTED] (b) (4) stated in Table 1-2 of Module 3.2.P.3.2.1.4.2 ([REDACTED] (b) (4)) appears to be [REDACTED] (b) (4) not in line with process capability.
- 5) Regarding the [REDACTED] (b) (4) drug product in the [REDACTED] (b) (4):
 - a) Modules 3.2.P.3.3.3 (Page 5, item 15), 3.2.P.3.3.7 (Page 7), and 3.2.P.3.4.1.4.1 (Page 9, Table 1-1 [REDACTED] (b) (4)) state that the allowable storage period [REDACTED] (b) (4). Clarify the allowable hold time and hold temperature.
 - b) Clarify whether bioburden and endotoxin testing will be routinely performed [REDACTED] (b) (4).

7) [REDACTED] (b) (4)

(b) (4)

8)

9)

10)

11)

- 12) Rabbit pyrogen test data as required in 21CFR610.13(b) were not provided in the BLA submission. Please submit the data from three drug product lots to demonstrate that the drug product does not contain pyrogenic substances.

13) Regarding shipping validation:

- a) Describe how EP2006 drug product manufactured at the Grenzach facility will be shipped to the U.S. Include the mode of transport, the drug product packaging configuration, and a summary of the shipping validation studies and data. The information should include the location of temperature probes during shipping validation and during routine transport.
- b) Submit a summary of the number and locations of the temperature probes used to record the data presented in Figure 9-1 of Report 3.2R, *Medical Device Part Summary of the Combination Product/Medical Device Aspects of EP2006_PFS_30_46* (b)(4). In the response specify the locations considered to be worst case.
- c) The data presented in Figure 9-1 indicates that the maximum allowable temperature of 8°C was exceeded for shipment (b)(4). Describe any product impact and how the deviation was resolved. Specify the maximum excursion temperatures and excursion duration.
- d) Submit validation studies demonstrating that the syringe stopper movement during shipping does not (b)(4). Describe the allowable distance that the syringe stopper can move before it (b)(4).

14) Regarding media fill simulation:

- a) Submit the microorganisms used for medium growth promotion testing.
- b) Submit the procedures conducted in the event of a media fill failure. In your response include a description of the impact of failure on product release and product fills.

15) Regarding endotoxin testing of EP2006 drug product:

- a) Submit a justification for why (b)(4) rather than EP2006 (b)(4) were used in the endotoxin recovery studies presented in SDN 9 (Module 1.11.1, eCTD sequence 0008).
- b) Submit the gel clot data for the endotoxin recovery studies presented in SDN 9.
- c) Submit the validation study report for determination of drug product endotoxin levels by the USP <85> kinetic chromogenic method. Include data supporting the maximum validation dilution and standard dilution for release testing.

16) Submit a description of the container closure integrity test (CCIT) method proposed for drug product stability testing in Module 3.2.P.8.2.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
09/17/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125553/0

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sandoz, Inc.
506 Carnegie Center Drive
Suite 400
Princeton, NJ 08540

ATTENTION: John Pakulski, RPh.
Head, US Biopharmaceutical Regulatory Affairs

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) dated and received May 8, 2014, submitted under section 351(k) of the Public Health Service Act for EP2006, 600 mcg/ mL.

We also refer to your May 23, 2014, correspondence, received May 23, 2014, requesting review of your proposed proprietary name, Zarxio.

We have completed our review of the proposed proprietary name, Zarxio and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your May 23, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Lara Akinsanya, Regulatory Project Manager in the Office of New Drugs, at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KELLIE A TAYLOR
08/14/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, August 13, 2014 5:54 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara
Subject: CDRH OC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 08/27

Hello John,

Please provide the following by **Wednesday, August 27, 2014** for FDA desk reviews of the Device component of the EP2006 300 mcg/0.5 mL and 480 mcg/0.8 mL solution for injection:

1. A detailed design control information describing where in your design and development process the device became subject to your design control program according to 21 CFR 820.30 Design Controls.
2. A detailed summary of how management with executive responsibility establishes its policy, objectives for, and commitment to quality in compliance with 21 CFR 820.20, Management Responsibility.
3. A detailed summary of procedures established and maintained to ensure that all purchased or otherwise received product and services conform to specified requirements as indicated per 21 CFR 820.50, Purchasing Controls.
4. A detailed summary of how corrective and preventive actions are identified, investigated, verified or validated, implemented, and documented in compliance with 21 CFR 820.100, Corrective and Preventive Action.
5. Clarification and details of which facilities in the submission are responsible for developing the design specifications of the device constituent part and maintenance of the design history file.

Please refer to suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations, available in the guidance document "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA

Staff," February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.ht>

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
08/13/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, August 05, 2014 3:30 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 8/22

Hello John,

Please respond to the below CMC Information Request by **Friday, August 22, 2014:**

1. Please provide a diagram showing the in-process bioburden and endotoxin sampling locations, the locations of the (b) (4), and the (b) (4) process. The bioburden of the manufacturing process should be monitored (b) (4).
2. Please implement an in-process bioburden limit for the (b) (4) step or justify the lack of in-process bioburden limit at that step.
3. Please provide information and microbiology validation data at scale for the proposed maximum hold times (b) (4).
4. Please include bioburden and endotoxin monitoring of the (b) (4) lifetime study at commercial scale. Provide the bioburden and endotoxin limits for the study.
5. The bioburden release test uses (b) (4) (b) (4) sample volume. Please update the bioburden specification to (b) (4). Similarly, the bioburden release test results should be expressed as CFU/volume tested.
6. With regard to bioburden release data provided in Section 3.2.S.4.4, "Batch analysis", 13 batches had results of (b) (4). Please provide the exact CFU/volume tested for those batches.
7. Please provide the summary qualification results for the bioburden test of the in-process and (b) (4) drug (b) (4). Please clarify if (b) (4) time is for the qualification samples or routine product bioburden samples.
8. With regard to the endotoxin qualification study of the (b) (4) (b) (4) sample, please provide the (b) (4) used for the (b) (4) calculation. Provide the summary qualification data for the (b) (4) (b) (4) sample. In addition, provide the dilution you will use for the routine testing of the (b) (4) (b) (4) sample.
9. With regard to the endotoxin qualification study (b) (4)

10. Please provide the bioburden and endotoxin limits (b) (4). In addition, provide microbiology validation data at scale for the maximum hold times (b) (4).
11. The (b) (4) endotoxin limit (b) (4) is too high based on the historical data. Please tighten the (b) (4) endotoxin limit (b) (4).

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
08/05/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125553/0

**FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED**

Sandoz Inc., a Novartis Company
Attention: John Pakulski, RPh
Head, Regulatory Affairs
US Biopharmaceuticals
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) dated May 8, 2014, received May 8, 2014, submitted under section 351(k) of the Public Health Service Act for EP2006.

EP2006 is a proposed biosimilar to Neupogen (filgrastim) (BLA 103353).

We refer to the July 7, 2014 filing notification letter informing you that your 351(k) BLA has been accepted for review with a standard review classification and a March 8, 2015 user fee goal date.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 8, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. For Protocol EP06-302, we identified 25 subjects who were treated with an alternate form of leukocyte growth factor rather than the assigned study agent. How these protocol violations affect the interpretation of the study results will be a review issue.

BLA 125553/0

Page 2

2. Your application requests licensure for 300 mcg/0.5 mL and 480 mcg/0.8 mL in single-use prefilled syringes only. Clarify how your prefilled syringe presentations can support dosing and administration in pediatric patients, such as young children with congenital neutropenia, who will require a daily subcutaneous injection. Your instructions for use of the prefilled syringe in the patient labeling do not address this circumstance.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Product Quality - CMC

1. You provided summary data of the qualification of the Master Cell Bank (MCB) and Manufacturer's Working Cell Bank (MWCb). Certificates of analysis for these cell banks were also provided. Update your submission to include full qualification reports for the MCB and MWCb, including bacteriophage testing.

2. Provide bacteriophage testing results of your current MWCb EP2006, (b) (4)

3. You provided an overview of the protocol for qualification of a future manufacturer's working cell banks (MWCb). Your protocol does not include comparability assessment of drug substance manufactured at full scale using approved and proposed MWCb's and lacks (b) (4)

(b) (4). The comparability data are needed to verify that EP2006 produced using a new MWCb is comparable to EP2006 produced using an approved MWCb. Update your protocol to include testing of drug substance manufactured at full scale with current and proposed MWCb's and to include (b) (4)

(b) (4) and submit the revised protocol for review.

4. (b) (4)

5. Based on the data provided in Section 3.2.S.5 Reference Standards or Materials, it appears that you have a one-tier reference material system. You should develop a two-tier in-house reference material system consisting of primary and working reference materials. Each subsequent working or primary reference material should be calibrated against an in-house primary material appropriately characterized that is representative of

BLA 125553/0

Page 3

production and clinical materials (ICH Q6B). Calibrating against a single primary reference material assures that the bioactivity determined for the test samples is consistent over time and limits the potential drift in product potency that may occur when each new standard is compared to the current working standard. To address this deficiency, provide a protocol for qualification of primary and working reference materials. Additionally, clarify the intended purpose(s) of your in-house primary/working reference materials (e.g. determination of potency, assay system suitability).

6. Your bioactivity assay for drug substance (EP2006-32s42-bioactivity-790-1-0) uses (b) (4) used in analytical procedure EP2006-32s42-bioactivity-790-1-0.
7. You propose a hold time (b) (4) You provided stability data for (b) (4) stored under these conditions at small scale and state that "stability (b) (4) was also proven by using (b) (4) stored up to (b) (4) for the production of drug substance and consecutively drug product leading to products which comply with the specifications and are similar to the batches produced with (b) (4). To further support the proposed hold time for (b) (4), provide the release, stability and characterization data (if available) of the DS and DP batches manufactured with the (b) (4) stored up to (b) (4) compared to DS and DP lots manufactured with (b) (4).

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit

BLA 125553/0

Page 4

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted a pediatric assessment with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Monsurat Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDVARDAS KAMINSKAS
07/22/2014

Wright, Kevin

From: Liu, Zhengyu <zhengyu.liu@sandoz.com>
Sent: Wednesday, July 16, 2014 5:11 PM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: Question on Request for Proprietary Name for BLA 125553

Hi Dr. Wright,

Thank you for your clarification. Good to know that re-evaluation is no longer required within the same review cycle.

Best regards, eddy

Zhengyu (eddy) Liu, Ph.D.
Regulatory Affairs
US Biopharmaceuticals, Sandoz Inc.
506 Carnegie Center, Suite 400
Princeton, NJ 08540
USA

Phone +1 609 6278679
Cell (b) (6)
Fax +1 609 6278659
zhengyu.liu@sandoz.com
www.novartis.com

From: Wright, Kevin [mailto:Kevin.Wright@fda.hhs.gov]
Sent: Wednesday, July 16, 2014 1:19 PM
To: Liu, Zhengyu
Cc: Kang, Sue
Subject: RE: Question on Request for Proprietary Name for BLA 125553

Dr. Zhengyu,

Please see my responses below.

From: Liu, Zhengyu [mailto:zhengyu.liu@sandoz.com]
Sent: Tuesday, July 15, 2014 1:53 PM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: Question on Request for Proprietary Name for BLA 125553

Dear Dr. Wright,

Thank you for your answer. I would like get one more clarification from you. According to FDA's practice, the trade name is **re-evaluated** 90 days before product approval (given the action date of March 8, 2015, reevaluation will probably happen in December 2014). DMEPA no longer re-evaluates proprietary names for marketing applications within a single application review cycle.

Assuming the decision is made to conditionally approve "Zarxio" by August 23, my understanding from your answer is that after reevaluation, if the acceptance is not overturned then the acceptance will become final and DMEPA won't issue a second letter. If the name is found acceptable, acceptance will be final for this review cycle and letter will be sent stating the proprietary name was found acceptable.

However if the acceptance is overturned after reevaluation, DMEPA will inform us right away. Is my understanding correct? If the name is found unacceptable, then we will notify you by letter.

Thank you very much.

Best regards, eddy

Zhengyu (eddy) Liu, Ph.D.
Regulatory Affairs
US Biopharmaceuticals, Sandoz Inc.
506 Carnegie Center, Suite 400
Princeton, NJ 08540
USA

Phone +1 609 6278679
Cell (b) (6)
Fax +1 609 6278659
zhengyu.liu@sandoz.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Friday, July 11, 2014 1:31 PM
To: Liu, Zhengyu
Cc: Pakulski, John; Kang, Sue
Subject: RE: Question on Request for Proprietary Name for BLA 125553
Importance: High

Dr. Liu,

Thank you for your inquiry. Please see my responses below.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 | kevin.wright@fda.hhs.gov

 Thinking green when printing

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.

From: Liu, Zhengyu [<mailto:zhengyu.liu@sandoz.com>]
Sent: Friday, July 11, 2014 12:14 PM
To: Wright, Kevin
Cc: Pakulski, John

Subject: Question on Request for Proprietary Name for BLA 125553

Importance: High

Dear Dr. Wright,

My name is Eddy Liu. I work for John Pakulski of Regulatory Affairs group from Sandoz. We submitted a Request for Proprietary Name for BLA 125553 in May. The proposed name "Zarxio" received an "conditional acceptable" opinion from FDA during IND phase in 2013. We have two questions regarding the name request:

1) Is DMEPA going to issue an opinion on the name within 90 days of receipt of the Request, i.e. by August 23? Yes, DMEPA will issue a decision on the proposed proprietary name by August 23.

2) When we approach the BLA action date of March 8, 2015, will DMEPA issue another comment on the name? If yes what is the approximate timeline?. No, DMEPA will not issue a second letter if the proposed proprietary name, Zarxio, is found acceptable by DMEPA.

Thank you for your help.

Best regards, eddy

Zhengyu (eddy) Liu, Ph.D.

Regulatory Affairs
US Biopharmaceuticals, Sandoz Inc.
506 Carnegie Center, Suite 400
Princeton, NJ 08540
USA

Phone +1 609 6278679
Cell (b) (6)
Fax +1 609 6278659
zhengyu.liu@sandoz.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Tuesday, May 20, 2014 3:14 PM
To: Pakulski, John
Cc: Kang, Sue; Akinsanya, Lara
Subject: BLA 125553 EP 2006: Request for Proprietary Name

Hello John,

This email is to notify you that Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to BLA 125553 if you intend to market this product with a proprietary name.

The request for proprietary name review should include FDA Form 356h, and a cover letter stating "REQUEST FOR PROPRIETARY NAME", on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

A complete request for proprietary name review should include the primary proprietary and where applicable the alternate proprietary name, intended pronunciation, derivation of proprietary name, and/or intended meaning of any modifiers (e.g. prefix, suffix) contained in the proprietary name.

Additionally, your request should include the following product characteristics: established name, prescription status, dosage form, product strength, proposed indication for use, route of administration, usual dosage, frequency of administration, dosing in specific populations, instructions for use, setting of use, storage requirements and the intended package configuration.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 kevin.wright@fda.hhs.gov

 Thinking green when printing

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN WRIGHT
07/17/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125553/0

FILING NOTIFICATION LETTER

Sandoz Inc., a Novartis Company
Attention: John Pakulski, RPh
Head, Regulatory Affairs
US Biopharmaceuticals
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) dated May 8, 2014, received May 8, 2014, submitted under section 351(k) of the Public Health Service Act for EP2006.

EP2006 is a proposed biosimilar to Neupogen (filgrastim) (BLA 103353).

We also refer to your amendments dated May 23, June 5, 12, 16, 18, 24 (2), and July 1, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. This filing communication constitutes the notification described in section 351(l)(2) of the Public Health Service Act that your 351(k) BLA has been accepted for review. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 8, 2015.

We plan to send a separate filing communication that provides additional information and describes any potential review issues identified during the initial filing review within 74 calendar days from the date of FDA receipt of the original submission in accordance with the performance goal established under the Biosimilar User Fee Act (BsUFA).

If you have any questions, call Monsurat Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

BLA 125553/0

Page 2

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.

Division Director

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
07/07/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, June 27, 2014 12:32 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara
Subject: ClinPharm Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 07/28

Hello John,

Please respond to the below Clinical Pharmacology Information Request by **Monday, July 28, 2014**:

- Regarding the G-CSF PK data from Study EP06-01, submit the individual concentration-time data and PK parameter data in a SAS-compatible dataset and variable definitions.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/27/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 25, 2014 11:45 AM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara
Subject: CMC Microbiology Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 7/1

Hello John,

Please respond to the below CMC Microbiology Information Request by **COB Tuesday, July 1, 2014:**

- 1) The EP2006 formulation contains excipients (b) (4) that could result in low endotoxin recovery (LER) (see K.L. Williams, Endotoxin Test concerns of Biologics, American Pharmaceutical Review, October 28, 2013). In the 11/14/2013 type 4 BPD meeting package response for IND 109197 (pages 14 and 15) you were advised to conduct studies regarding the effect of hold time on endotoxin recovery for (b) (4) (b) (4) spiked with known amounts of endotoxin in containers with compositions similar to those used for manufacture and sampling. This information was not provided. Please submit.

- 2)  (b) (4)
- 3)  (b) (4)

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/25/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, June 24, 2014 8:02 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara
Subject: CMC Information Request (device) - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen

Hello John,

Please respond to the below CMC Information Request as soon as the information is available:

We note that the United States Pharmacopeial Convention recently published a monograph for filgrastim in United States Pharmacopeia 36 -National Formulary 31, Supp. 2 (official 12/1/13). FDA has not yet determined whether the USP monograph for filgrastim is applicable to your proposed biosimilar product. However, we request that you describe whether your proposed biosimilar product meets the standards set forth in the monograph.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/25/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, June 20, 2014 3:44 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara; Liu, Zhengyu (zhengyu.liu@sandoz.com)
Subject: Clinical Information Request (device) - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/24

Hello John,

Please respond to the below Clinical Information Request regarding the delivery device by **June 24, 2014**:

The submission contains basic technical information regarding the container closure system. The provided information references separate DMF's for the syringe barrel/hypodermic needle and the plunger rod/rubber stopper; however, there is no information provided regarding any functional testing that has been conducted on the final, finished device. FDA requires that functional testing be provided for the final, finished device in order to adequately review all characteristics of the device. FDA Guidance "Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4" provides an overview of functional testing that is recommended for a product of this type (in particular, please see Section V.B.3).

Please provide the requested testing for review.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/21/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, June 16, 2014 11:56 AM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara; Liu, Zhengyu (zhengyu.liu@sandoz.com)
Subject: Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/24

Hello John,

Please respond to the below Clinical Information Request by **June 24, 2014**:

- I. Provide a copy of the study protocol and amendments for Study Protocols 101, 103 and 109, respectively, and a corresponding sample Case Report Form (CRF), as applicable.
- II. Provide a copy of the sample informed consent form and amendments for Study Protocols 101, 103 and 109, respectively.
- III. Provide study patient data listings organized by clinical site number to include the elements below in PDF electronic format. The PATIENT DATA LISTINGS should be GROUPED and submitted to the Agency according to CLINICAL STUDY SITE (PER COUNTRY). The study subject data listings should capture the following, as applicable:
 - 1) Subject discontinuation (If applicable per treatment group: site subject number, screening visit date, informed consent date, assent date, date of first dose/last dose, length of date or discontinuation, reason for discontinuation).
 - 2) Prohibited medications (non-study medications): (If applicable per treatment group: site subject number, type (prohibited meds), medication (preferred term), indication/reason taken, date started, date stopped).
 - 3) Adverse events, (If applicable per treatment group: preferred term/investigator entry, detailed drug name, blinded-phase active dose, date start/stopped, severity/resolution, Serious Adverse Event (yes, no), death (yes/no)).
 - 4) Clinical, laboratory and other diagnostic safety events or endpoints, as applicable: (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1...etc).
 - 5) G-CSF, CD34 and anti-rhG-CSF antibody assay laboratory testing and results as applicable to the study protocol.
 - 6) Clinical, laboratory and other data relevant to the primary efficacy endpoints: body temperature, neutrophil counts (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1...etc).
 - 7) Protocol deviations.

For Part III, the requested patient data listings are for the following clinical study sites:

1. Ralf Freese, Hamburg, Germany, Protocol 101
2. U. Fuhr, Kol, Protocol 103
3. F. Sorgel, Protocol 101,103,109 and 302
4. Richard Larouche, Montreal, Canada, Protocol 109
5. Caroline Hebert, Protocol 109
6. Vera Koppenburg , Protocol 109 and 302
7. Josef Cseh, Szekesfehervar, Hungary, Protocol 302 Site 204
8. Irina Davidenko, Krasnodar, Russia, Protocol 302 Site 703 (n=29 enrolled patients)
9. Vladimir Semiglazov, St. Petersburg, Russia, Protocol 302 Site 706 (n=44 enrolled patients)

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/17/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 11, 2014 4:24 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara; Liu, Zhengyu (zhengyu.liu@sandoz.com)
Subject: Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/16

Hello John,

Please respond to the below Clinical Information Request by **June 16, 2014**:

1. Please review the clinical trial site contact list attached. Please update the contact information for each site. Note that for the clinical trial sites, we are seeking the contact information for the study subjects' medical records (primary source documentation) and for the investigator's study records.
2. For each of the 13 clinical protocols submitted to the BLA, please provide contact information for the site where the sponsor's records will be available for inspection.
3. For each of the 13 clinical protocols submitted in the BLA, please provide a copy of the final version of the protocol that incorporates all interim amendments.
4. We noted that for protocol EP06-302, the deviation file indicates that multiple subjects were treated with G-CSF products other than US-Neupogen or EP2006, but the exposure file ex.xpt shows that all subjects received only study drug. Please provide a corrected version of ex.xpt for protocol EP06-302 that includes one additional column that specifies exactly which G-CSF (manufacturer/brand) was administered each date for each subject. Please also clarify whether a G-CSF product not specified in the protocol was used (as a protocol deviation) in any of the other clinical trials submitted to the BLA.



Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Site # (Name,Address, Phone number, email, fax#)	Responsibility
<p>Ralf Freese, M.D. MDS Pharma Services, Hamburg Clinical Trial Center North Martinistrasse 52. S10 D-20246 Hamburg. Germany Phone: +49 (0) 40 42803 1602 Fax: +49 (0) 40 42803 1605 email:</p>	<p>Protocol 101 Clinical Site</p>
<p>U. Fuhr, M.D. ITECRA GmbH&Co KG c/o Evangelisches Krankenhaus Weyertal, 7th floor Weyertal 76 50931 Köln, Germany Phone: +49 - 221 - 4 78 52 30 FAX: +49 - 221 - 4 78 70 11 email:</p>	<p>Protocol 103 Clinical Site</p>
<p>(b) (4)</p>	<p>G-CSF and CD34 assay results</p>
<p>Richard Larouche, M.D. PharmaNet Canada Inc. 5160, boul. Décarie, Suite 800 Montréal (Québec), Canada H3X 2H9 Tel.: 001 (514) 485-7500 Fax: 001 (514) 485-7501 email:</p>	<p>Protocol 109 Clinical Site</p>
<p>(b) (4)</p>	<p>CD34 assay results</p>
<p>Dr. Vera Koppenburg HEXAL AG Keltenring 1+3 82041 Oberhaching Tel.: +49 89 61 36 70 -135 Fax.: +49 89 61 36 70 -147 email: vera.koppenburg@sandoz.com</p>	<p>Anti-rhG-CSF antibodies</p>
<p>Site 204 Jozsef Cseh MD Fejer Megyei Szent Gyorgy Korhaz, Onkologiai Osztaly 8000 Szekesfehervar, Seregelyesi u. 3. Telephone +36 22 535 662 Fax +36 22 535 667 email: onkologiaf@mail.fmkorhaz.hu</p>	<p>Protocol 302 Clinical Site</p>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/11/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, June 09, 2014 12:32 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara
Subject: CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/13

Hello John,

Please respond to the below CMC Information Request by **June 13, 2014**:

1. You provided analytical similarity data of EP2006, US-licensed Neupogen, and EU-approved filgrastim in three separate documents (“Biosimilarity with reference product”, “Biosimilarity EU Comparator” and “additional Data Neupogen”). To facilitate the review of these data, please provide all the analytical similarity results (e.g. release, stability and characterization data, including functional studies) in a tabular side-by-side format comparing the three products. Representative primary data (e.g., chromatograms, spectra, electropherograms) and graphical representation of the data (when applicable) should also be provided in a side-by-side format comparing the three products. Additionally, please identify in the tables, figures and representative primary data the “version” of EP2006 included in the studies. These data should be located in a single section in 3.2.R.
2. A comparability report for the transfer of drug product from IDT PFS to GPG PFS was provided in the BLA. These data are intended to support the comparability of EP2006 used in clinical studies 104, 105 and 109 (IDT PFS) to the proposed commercial EP2006 drug product (GPG PFS). In addition to clinical studies 104, 105 and 109, you provided data from other clinical studies (e.g. 101, 102, 103, and 301) and preclinical studies using different “versions” of EP2006 (e.g. LEK vial and PFS) to support your application. In order to justify the relevance of the clinical and pre-clinical data from these studies, comparability between each “version” of EP2006 used in the clinical and pre-clinical studies and the proposed commercial drug product (GPG) should be demonstrated. We acknowledge that some of the analytical data for the early “versions” of the drug product were provided in section 3.2.P.5.4 and 3.2.P.8. In order to facilitate review of these data, please provide all the analytical data intended to support comparability of the proposed commercial drug product and the drug product used in all the clinical and pre-clinical studies intended to support your application in a side-by-side format comparing all “versions” of the EP2006 drug product. Representative primary data (e.g. chromatograms, spectra, electropherograms) and graphical representation of the data (when applicable) should also be provided in a side-by-side format. These data should be located in a single section in 3.2.R.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products

Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/09/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 04, 2014 10:54 AM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara; Tzeng, Linhua
Subject: Statistics Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/10

Hello John,

Please respond to the below Statistics Information Request regarding Study EP006-302 by **June 10, 2014**:

- Perform subgroup analyses to assess whether results are consistent across subgroups. Currently, you have not submitted them.
- Submit all programs (e.g. SAS) that were used to create the efficacy endpoints, all of the efficacy, safety tables, and figures included in the main test portion of the CSR and in the label.
- Provide ITT flag in your dataset ADEFFIC.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
06/04/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, May 29, 2014 10:43 AM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara; Tzeng, Linhua
Subject: CMC Information Request- BLA 125553 for EP2006 (proposed biosimilar to Neupogen) DUE 6/10

Hello John,

Please respond to the below Clinical Information Request by **June 10, 2014**:

- We are planning to conduct a pre-license inspection of your drug substance manufacturing site (Sandoz, Kundl, Austria) in support of BLA STN125553. The manufacturing facility should be in operation for the production of EP2006 during the inspection. Ideally, the facility should be in operation during the September-November timeframe (2014) in order to meet all review milestones. Please provide a manufacturing schedule for EP2006 drug substance.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
05/29/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, May 22, 2014 5:11 PM
To: Pakulski, John (john.pakulski@sandoz.com)
Cc: Akinsanya, Lara; Tzeng, Linhua
Subject: Clinical Information Request- BLA 125553 for EP2006 (proposed biosimilar to Neupogen) DUE 6/5

Hello John,

Please respond to the below Clinical Information Request by **June 5, 2014**:

1. Please provide define files for the datasets for all clinical studies submitted in the BLA. Either a pdf or html version (with appropriate hyperlinks) would be acceptable. For additional information about the define files, please see sections 3.1.2.1 and 3.1.2.2 of “Study Data Specifications” available at:
<http://wcms.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>
2. Please ensure that the define files include the MedDRA version number and AE grading system used in the respective data sets.
3. For Protocol EP06-302, the datafile ex-ep06-302.xpt, which lists drug exposure, includes multiple rows for study visits with no drug dose, start date or end date. Please explain why these data fields are blank. If the blank fields are in error, please submit a corrected datafile.
4. Protocols EP06-109 and EP06-302 are foreign clinical trials. Please describe your rationale for assuming that the data from these trials are applicable to the US population.
5. The clinical study reports indicate that 4 sites were audited for Protocol EP06-109 and 16 sites for Protocol EP06-302, but the report does not discuss the findings. Please identify any substantial issues identified in your audits, what corrective actions, if any, were required, and whether implementation of the corrective actions as applicable were successful.
6. For Protocol EP06-302:
 - a) Please confirm that the protocols were approved by the IECs at each institution.
 - b) Please confirm that you have on file written commitment to ensure GCP from each investigator.
 - c) Please provide a description of the monitoring procedures that were used to ensure compliance with GCP.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

(301) 796-9634 (phone)

(301) 796-9849 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
05/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125553/0

BLA ACKNOWLEDGEMENT

Sandoz Inc. a Novartis Company
Attention: John Pakulski, RPh
Head Regulatory Affairs
US Biopharmaceuticals
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Mr. Pakulski:

We have received your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: “(b) (4) / “EP 2006-filgrastim,” proposed biosimilar to Neupogen (filgrastim)

Date of Application: MAY 8, 2014

Date of Receipt: MAY 8, 2014

Our Secondary Tracking Number (STN): BLA 125553/0

Proposed Use: Cancer patients receiving myelosuppressive chemotherapy,
Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy,
Cancer patients receiving bone marrow transplant,
Patients undergoing peripheral blood progenitor cell collection and therapy, and
Patients with severe chronic neutropenia

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act

BLA 125553/0
Page 2

by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 125553/0** submitted on May 8, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

BLA 125553/0
Page 3

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Monsurat Lara Akinsanya, MS
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
05/21/2014

Wright, Kevin

From: Pakulski, John <john.pakulski@sandoz.com>
Sent: Tuesday, May 20, 2014 3:38 PM
To: Wright, Kevin
Subject: RE: BLA 125553 EP 2006: Request for Proprietary Name

Hi Kevin,

I am acknowledging receipt and confirming that we will submit Request for Proprietary Name.

Best regards, John

John M. Pakulski, R.Ph.
Executive Director and Head US Biopharmaceutical Regulatory Affairs
Sandoz Inc., a Novartis company
506 Carnegie Center, Suite 400
Princeton, NJ 08540
USA
Phone: +1 609 627 8861
Cell: (b) (6)
Email: john.pakulski@sandoz.com
Web: <http://www.novartis.com>

Learn more about biosimilars @ www.sandoz-biosimilars.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Tuesday, May 20, 2014 3:14 PM
To: Pakulski, John
Cc: Kang, Sue; Akinsanya, Lara
Subject: BLA 125553 EP 2006: Request for Proprietary Name

Hello John,

This email is to notify you that Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to BLA 125553 if you intend to market this product with a proprietary name.

The request for proprietary name review should include FDA Form 356h, and a cover letter stating “REQUEST FOR PROPRIETARY NAME”, on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

A complete request for proprietary name review should include the primary proprietary and where applicable the alternate proprietary name, intended pronunciation, derivation of proprietary name, and/or intended meaning of any modifiers (e.g. prefix, suffix) contained in the proprietary name.

Additionally, your request should include the following product characteristics: established name, prescription status, dosage form, product strength, proposed indication for use, route of administration, usual dosage,

frequency of administration, dosing in specific populations, instructions for use, setting of use, storage requirements and the intended package configuration.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 kevin.wright@fda.hhs.gov

 Thinking green when printing

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN WRIGHT
05/30/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 109197

MEETING MINUTES

Sandoz Inc.
Attention: John M. Pakulski
Head Regulatory Affairs
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Pre-Investigational New Drug Application (PIND) file for EP2006.

We also refer to the meeting between representatives of your firm and the FDA on November 19, 2013. The purpose of the meeting was to discuss the format and content of the planned BLA to support licensure of EP2006, a proposed biosimilar to US-licensed Neupogen, under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, M.D., Ph.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: November 19, 2013; 10:00 AM – 11:00 AM EDT
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: PIND 109197
Product Name: EP2006 (proposed biosimilar to US-licensed Neupogen)
Indication: EP2006 is being developed for the same indications as approved for US-licensed Neupogen
Sponsor/Applicant Name: Sandoz Inc.

Meeting Chair: Albert Deisseroth, M.D., Ph.D.
Meeting Recorder: Lara Akinsanya, M.S.

FDA ATTENDEES

Division of Hematology Products (DHP)

Ann T. Farrell, M.D., Division Director
Albert Deisseroth, M.D., Ph.D., Clinical Team Leader
Thomas Herndon, M.D., Medical Officer
Lara Akinsanya, M.S., Senior Regulatory Health Project Manager

Division of Hematology Oncology Toxicology (DHOT)

Haleh Saber, Ph.D., Supervisory, Pharmacologist
Pedro DelValle, Ph.D., Pharmacology/Toxicologist Reviewer

Office of Pharmaceutical Science, Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP)

Gibbes Johnson, Ph.D., Team Leader, Product Quality
Maria Gutierrez Lugo, Ph.D., Product Quality Reviewer

Office of Clinical Pharmacology (OCP)

Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader
Sarah Schrieber, Pharm.D., Clinical Pharmacology Reviewer

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

Office of Biostatistics, Division of Biometrics V (DBV)

Yuan Li Shen, Ph.D., Statistical Team Leader
Qing Xu, Ph.D., Statistician

Office of Pharmaceutical Science, Office of Biotechnology Products (OBP), Biotechnology Manufacturing Assessment Branch (BMAB)

Bo Chi, Ph.D., Team Leader, Product Quality
Patricia Hughes, Ph.D., Product Quality Reviewer

Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Team (TBBT)

Leah Christl, Ph.D., Associate Director for Therapeutic Biologics
Sue Lim, M.D., Senior Staff Fellow
Neel Patel, Pharm.D., Regulatory Project Manager
Tyree Newman, BS, Senior Regulatory Project Manager
Carla Lankford, M.D., Ph.D. Science Policy Analyst

Office of Regulatory Policy (ORP)

Janice Weiner, J.D., M.P.H., Senior Regulatory Counsel

Center for Device and Radiological Health (CDRH)

LCDR Quynh Nhu Nguyen, Regulatory Reviewer (Human Factor)

SPONSOR ATTENDEES

Sandoz Inc:

- Carlos Sattler, Vice President, Clinical Development and Medical Affairs
- John Pakulski, Head Regulatory Affairs, US Biopharmaceuticals
- Zhengyu Liu, Team Leader Regulatory Affairs, US Biopharmaceuticals
- Deborah Ablordeppey, Associate Regulatory Affairs, US Biopharmaceuticals

Sandoz GmbH:

- Mark McCamish, Global Head Biopharmaceutical Development
- Pascale Burtin, Head Global Clinical Development Biopharma
- Sigrid Balser, Global Head Biostatistics and Clinical Submission Management
- Jens Schletter, Head of Global Regulatory CMC
- Roumen Nakov, Head Clinical Development Hematology
- Ulrich Kronthaler, Preclinical Development Manager
- Stefan Kramer, Global Program Leader

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

- Hannes Wallnoefer, Regulatory Affairs Manager
- Ursula Krimm, Regulatory CMC Team Leader
- Daniela Pfister, Regulatory CMC Manager
- Katharina Ledermaier, eCTD Business expert

External Consultant (Device Expert) – (b) (4)

- (b) (4)

1.0 BACKGROUND

On August 22, 2013, the Agency received a meeting request from Sandoz to discuss the format and content of the planned BLA for Sandoz's rhG-CSF product, EP2006, to support licensure as a biosimilar to US-licensed Neupogen under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)). The Agency granted the meeting request on September 7, 2013, as a Biosimilar Biological Product Development (BPD) Type 4 Meeting.

On November 14, 2013, the Division emailed Sandoz the preliminary responses to the questions contained in the meeting information package received August 22, 2013.

2. DISCUSSION

General Introductory Comments:

FDA may provide further clarifications of, or refinements and/or changes to, these preliminary responses and the advice provided at the meeting based on further information provided by Sandoz and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the PHS Act.

Please note that for ease of reference and discussion, we have renumbered your questions in sequential order.

2.1 Electronic submission – eCTD

Sandoz intends to submit the initial application in electronic form using the eCTD format according to current FDA requirements. In the following the applicant would like to take the chance to point out Sandoz' position and strategy on eCTD.

The applicant will provide a "reviewer's guide" as appendix to the cover letter with the initial submission containing information on the content, hyperlinking strategy, naming conventions, legacy documents, literature references, metadata etc., in order to facilitate a smooth and convenient review of the application for the Agency.

Because Sandoz pursues a global development, it proposes to provide all documentation in

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

A4 format while guaranteeing that the page layout is compatible with letter format. In other words, all documents will be suitable for printing on letter format paper as well as A4 format paper. Page margins follow the specifications in the guideline (PDF Portable Document Format (PDF) Specifications).

Question 1:

Annotated table of contents

Sandoz intends to submit an electronic CTD dossier as required by the FDA. In the briefing package submitted together with this meeting request, a table of contents of the dossier is provided as Table 13-1. A brief description of all documents is included into this table of contents.

Does the Agency agree that the proposed documents as described are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required, which have to be included in the eCTD dossier for an application under section 351(k) of the Public Health Service Act?

FDA Response:

No, we do not agree that your proposal is adequate. Please see the responses to the remaining questions for information on additional documents and information that should be included in your planned eCTD submission.

Discussion:

No discussion occurred.

Question 2:

Scanned PDFs – OCR

Some existing documents such as literature references or CRF's are not available in a searchable format (i.e. not created from a readable source or OCR).

Does the Agency agree that it is acceptable to include these documents in the biosimilar BLA submission as "non-searchable" PDF documents?

FDA Response:

Yes, we agree.

Discussion:

No discussion occurred.

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

Question 3:

Hyperlinking

Sandoz intends to use efficient inter-document hyperlinking between individual dossier documents, besides adequate intra-document hyperlinking. This will facilitate a quick and convenient review. Hyperlinking is planned within Modules 2 and 3 and from Module 2 to the respective sections in Modules 3, 4, and 5. It is not planned to hyperlink documents within Modules 4 and 5 or across Modules 3, 4 and 5 to keep the number of hyperlinks to a reasonable amount.

Does the Agency agree with the proposed hyperlinking strategy?

FDA Response:

No, we do not agree. Please provide hyperlinks within Module 5.

Discussion:

No discussion occurred.

2.1 CMC

Question 4:

Does the Agency agree that the CMC data package is sufficient to permit review of the registration application?

FDA Response:

No, we do not agree. We have insufficient information to determine if the CMC data package is sufficient to permit meaningful review of the BLA. Furthermore, you stated that you intend to include “only selected information of the data packages” in the CTD (page 27). We advise that the CMC data and information expected for review of the proposed biosimilar product should be included in the BLA.

Based on the limited CMC information you have provided, we have identified the following issues:

- 1. The “final” analytical similarity assessment strategy, as outlined in the response to our information request dated November 1, 2013, intended to demonstrate that EP2006 is analytically “highly similar” to the reference product, US-licensed Neupogen, and to support an analytical bridge between EP2006, US-licensed Neupogen and the EU-approved filgrastim product (marketed in the EU as “Neupogen”) is based on limited data. We have identified deficiencies including limited product characterization (e.g. lack of tests to evaluate product strength and disulfide bond integrity, and insufficient orthogonal methods for characterization of aggregates and higher order structure) and limited number of lots of EP2006, US-licensed Neupogen and the EU-approved**

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

filgrastim product analyzed. We note that the data may not be sufficient to support a demonstration of “highly similar” or to build an adequate scientific bridge.

In your response to the information request, you state that you “compare your biosimilar products to the reference product throughout the development process on many more lots over time”. The comparative analytical data generated during development may be considered to support analytical similarity provided the analytical characterization of the products is robust, sufficient lots of EP2006, US-licensed Neupogen and the EU-approved filgrastim product were evaluated, and the EP2006 material used in the assessment includes EP2006 product manufactured by the clinical process and by the proposed commercial process for which you seek approval.

- 2. We note that you have made changes to the manufacture of EP2006 drug substance and drug product (e.g. scale and site of manufacture), and plan to submit comparability data in your BLA submission. Please be aware that in addition to demonstrating comparability between the pre-change and post-change drug substance (DS) and drug product (DP), analytical similarity of EP2006 manufactured by the clinical processes (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at Lek Pharmaceuticals d.d., Slovenia and IDT Biologika GmbH, Germany) and proposed commercial product (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at GP Grenzach Produktions GmbH, Germany) needs to be demonstrated to US-licensed Neupogen.**

You plan to submit analytical data comparing EP2006, US-licensed Neupogen and the EU-approved filgrastim product to demonstrate analytical similarity of your product to the reference product, US-licensed Neupogen, and to establish an analytical bridge between EP2006, US-licensed Neupogen, and the EU-approved filgrastim product. In your BLA submission, clearly specify the data you intend to use to demonstrate analytical similarity and the data intended to establish the analytical bridge between your product, the reference product, and the EU-approved filgrastim product. For the analytical bridge, we expect all three comparisons (EP2006 to US-licensed Neupogen, EP2006 to the EU-approved filgrastim product, and the EU-approved filgrastim product to US-approved Neupogen) to meet the pre-specified acceptance criteria for similarity. Additionally, specify whether the analytical similarity assessment was conducted with EP2006 lots manufactured by the clinical and proposed commercial processes.

With respect to organization of the CMC data package, address the following in the BLA submission:

- 1. Module 3 should also include the following data:**
 - i. You propose to provide “Executed Batch Records” upon request. This is not acceptable. Executed batch records should be provided in the BLA submission.**

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

- ii. **You plan to provide analytical method validation reports for non-compendial methods in Module 3 section 3.2.S.4.3. These reports along with method validation protocols should be located in the regional section (3.2.R)**
- iii. **Table 13-1 does not specify whether analytical comparability and analytical similarity protocols will be provided. Provide analytical comparability and analytical similarity protocols in separate 3.2.R modules.**
- iv. **Functional assays, including mechanism of action, should be provided and a justification that EP2006 has the same mechanism(s) of action as US-licensed Neupogen needs to be included in your BLA submission. Provide a summary of the data under Module 2.6 (“Nonclinical Written and Tabulated Summaries”) and Module 2.3 (“Quality Overall Summary”) with a link to the relevant section(s) of Module 3.**

2. In addition, include the following additional information in the relevant CTD sections.

CTD section	Comment
1.1.2 FDA form 356h	Indicate if the manufacturing and testing sites are ready for inspection.
1.3 Administrative information	A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections. Environmental Assessment or a request for categorical exclusion
2 Common Technical document summaries	Summaries of “Executed Batch Records” and summaries of “Analytical Comparability and Analytical Similarity protocols”
3.2.S.2.5 Process validation and/or evaluation	<ul style="list-style-type: none"> • Three successful consecutive (b) (4) hold time validation runs at manufacturing scale from microbiology perspective. • Information (b) (4) including microbiology data • Data summaries of shipping validation studies
3.2.S.4.3 Validation of analytical procedures	Qualification reports for bioburden and endotoxin tests.
3.2.P.3.5 Process validation and/or	<ul style="list-style-type: none"> • (b) (4) retention study report (b) (4)

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

<p>evaluation</p>	<div style="background-color: #cccccc; height: 100px; width: 100%;"></div> <div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <ul style="list-style-type: none"> • Hold time validation at scale from microbiology perspective <div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <ul style="list-style-type: none"> • Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs, • A description of the routine environmental monitoring program • Shipping validation data, including container closure integrity data
<p>3.2.P.5.3 Validation of analytical procedures</p>	<p>Qualification of bioburden, endotoxin, and sterility tests. Results of rabbit pyrogen test using three drug product lots.</p>
<p>3.2.P.8.2 Post-approval Stability Protocol and Commitment</p>	<p>Container closure integrity test (b) (4) on the stability program.</p>
<p>3.2.A Appendices</p>	<p>Information about other products manufactured in the facilities and strategies to prevent contamination and cross-contamination should also be described in this section.</p>

Discussion:

The sponsor presented the attached slide presentation. The sponsor presented slides 10 – 32 in relation to the FDA response to Questions 4, 7, and 11, and asked the following clarification questions:

Is the information sufficient to address the concerns raised in the written feedback regarding the analytical links for EP2006 used across the clinical program?

Does the Agency agree that the proposed CMC data for the EP2006 vials establishes an appropriate relationship to the proposed commercial material such that clinical study EP06-302 can be considered pivotal?

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

The FDA acknowledged that the information presented by Sandoz in the slide presentation was more robust than the “final similarity assessment” data that was provided in the meeting briefing package. The FDA noted that the additional data, as presented, appears reasonable to address their concerns raised in the responses to the questions regarding the limited product characterization and limited number of lots. The FDA noted that the submission of the data package as outlined in the slide presentation appears more likely to support a demonstration of “highly similar” and to build an adequate scientific bridge, as described in the response to Question 4; however, the Agency would need to review the data to determine whether the data fully addressed the FDA’s concerns. FDA noted that multiple comparability exercises were conducted since the completion of the clinical studies in 2004.

The sponsor noted that lots of US-licensed Neupogen and EU-approved filgrastim were collected and tested over a period spanning several years. The FDA advised the Sponsor to provide information about the number of lots tested and lot information, including but not limited to the lot expiry date and testing date, with the data used to determine the lot-to-lot variability of US-licensed Neupogen, EU-approved filgrastim, and EP2006. The sponsor was also advised to provide sufficient data and justification to establish an adequate analytical bridge between US-licensed Neupogen and EU-approved filgrastim. The FDA referred the sponsor to FDA’s response to Question 4 regarding the expectation of the three pair-wise comparisons among the three products. FDA noted that building an acceptable analytical bridge would be critical to justify the relevance of clinical data generated with EU-approved filgrastim, including the multiple dose data supporting the mobilization indication. In addition, the FDA noted that multiple comparability exercises were conducted with EP2006 since the completion of the clinical studies comparing EP2006 to EU-approved filgrastim in 2004 in order to evaluate and support manufacturing changes to EP2006. The FDA stated that the multiple comparability exercises would add complexity to building an adequate analytical bridge to justify the relevance of clinical data generated using EP2006 pre-change material. The FDA advised Sandoz to clearly identify the data being used to support comparability of the EP2006 material used in the clinical studies to the EP2006 material intended for commercial marketing in the US.

The sponsor noted that additional analytical tests using retained samples of the drug product and drug substance lots used in the clinical trials would not be possible. These lots surpassed the (b) (4) shelf life years ago, as these studies were started in 2004 to support the EMA MAA application.

Clinical study EP06-302 was conducted with EP2006 in a vial presentation. The FDA noted that this represented a change in the container-closure system to that of the proposed EP2006 commercial product, which will be presented in pre-filled syringes-(PFS). The sponsor noted that no formal comparability exercise was performed between the EP2006 PFS and EP2006 vials. FDA advised that the sponsor would need to build a bridge between the EP2006 PFS and vials in order to justify the relevance of the data generated using the vial presentation to the PFS presentation, and that it was not acceptable to have no comparability assessment between the PFS and the vials. In order to build a bridge between the EP2006 PFS and vials,

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

a head-to-head comparability exercise should be performed as per ICH Q5E to establish the relationship (i.e., comparability) between the PFS and vial products.

The sponsor clarified that they do not intend to seek licensure for EP2006 in the vial presentation [REDACTED]. As such, the sponsor stated their position that certain tests, such as stability testing, should not be part of the comparability exercise between the PFS and vials recommended by FDA. FDA acknowledged the sponsor's position, and stated that a targeted analysis that includes select methods may be acceptable, but the attributes that are evaluated and methods which are used should be justified. The FDA noted that evaluation of leachables should be included as part of the comparability exercise.

FDA noted that Sandoz should clearly identify in the BLA what data are being used to support a demonstration of similarity and what data are being used to support comparability.

Question 5:

Does the Agency concur with Sandoz' proposal to provide the detailed summary reports for biosimilarity studies with the originators as well as the comparability studies performed for quality changes during development as separate 3.2.R modules?

FDA Response:

Your proposal to provide analytical similarity reports and analytical comparability reports as separate 3.2.R. modules is acceptable. However, full analytical similarity, and analytical comparability reports should be provided. Please refer to comment 3 in the response to question 1 above regarding the content of the analytical similarity and analytical bridge data.

Discussion:

No discussion occurred.

Question 6:

Does the Agency concur with Sandoz' proposal to include more detailed information on the process characterization as separate 3.2.R module(s) (e.g. detailed description of methodology and specific examples from process characterization studies)?

FDA Response:

Yes, we concur.

Discussion:

No discussion occurred.

Question 7:

Sandoz will provide information on several supportive clinical studies (see also Clinical Question 5). These studies were conducted using [REDACTED] which is different from the product Sandoz is seeking approval for ([REDACTED])

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

Does the Agency agree with Sandoz's proposal that inclusion of CMC data on (b) (4) used in supportive clinical studies is not needed?

FDA Response:

No, we do not concur. The purpose of the "supportive clinical studies" is not clear from the information provided in your meeting package. Therefore, it is unclear whether the associated CMC data are required in the BLA. In the event the "supportive clinical data" generated with the different (b) (4) material are required to support your 351(k) application, sufficient CMC data should be provided to establish the relationship between such (b) (4) material and the EP2006 product for which you seek approval.

Discussion:

See summary of discussion captured under Question 4.

Question 8:

The product concerned is considered a combination product composed of the drug and two device components, in particular a pre-filled syringe and a needle safety guard (b) (4). Sandoz proposes to submit information on the pre-filled syringe and the needle safety guard, and their respective interfaces in a summary document in section 3.2.R of the eCTD. To avoid redundant information, appropriate hyperlinks to Module 3.2.P documents will be set and the respective information will not be repeated in Module 3.2.R. As requested during the pre-IND meeting (see pre-IND meeting minutes dated 28 October 2010), Sandoz will provide objective evidence that the device components can be handled safely and effectively by the intended user groups consisting of patients, healthcare professionals, and caregivers. The summary report that Sandoz intends to provide is based on a simulated use handling study conducted by Novartis Pharma AG for a combination product composed of the identical device components (i.e. pre-filled syringe, needle safety guard) and comparable instructions for use regarding the Novartis product. This study revealed that all intended user groups can safely and effectively handle the device. Although the patient population differs between the Novartis product and EP2006 it can be safely assumed that the device components also suits EP2006 users, because they don't have any special needs from a human factors perspective that is caused by the disease (e.g. such as patients suffering from rheumatoid arthritis (RA)).

Does the Agency concur that the outlined approach to address the requirements for the presented combination product EP2006 is acceptable?

FDA Response:

You stated that that you will provide a summary from a simulated use study that was conducted with a Novartis product. In addition, you stated that the device components (pre-filled syringe and needle safety guard) are identical to the Novartis product. However, it appears that the patient population differs between the Novartis product and EP2006. Different patient population indicates different intended user group. A key component of

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

human factors/usability validation testing is that users who are representative of actual users be used for the testing.

At this time, we cannot determine whether your approach is acceptable without information that provides a comprehensive analysis of the intended users for your product and how they are comparable to the users of the Novartis product, and without a comprehensive use-related risks analysis on the use of your product. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

You should submit these detailed analyses for review. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

Discussion:

The sponsor presented the attached slide presentation. The sponsor presented slides 33-35 in relation to the FDA response to Question 8.

FDA noted that the information and approach presented by the sponsor in the slide presentation would need to be discussed internally, and that FDA would provide comments in a post-meeting note.

Post Meeting Note: You clarified at the meeting that the proposed device is identical to the Novartis device. You also clarified that you intend to use existing human factors data from healthy subjects that were collected using the Novartis device to support the human factors evaluation for the proposed device.

This approach is acceptable. However we advise you that a detailed discussion on how you intend to use the human factors data obtained from existing studies to support the proposed product and a justification as to why existing human factors data are relevant for the proposed product should be included in the BLA. As part of the justification, you may consider providing a comparison of the user interface, intended users, and uses for the two products.

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

2.3 Pharmacology/Toxicology

Question 9:

Does the Agency agree that the pharmacology and toxicology package summarized in Table 12-1 is sufficient to permit assessment of biosimilarity at the nonclinical level and the review of the respective sections of proposed biosimilar BLA dossier?

FDA Response:

Yes. The pharmacology and toxicology package is acceptable for BLA filing. However, a final determination of biosimilarity will be made during the BLA review based on the totality of the evidence submitted.

Discussion:

No discussion occurred.

Question 10:

Does the Agency agree that for licensure of EP2006 as a biosimilar product to Neupogen under 351(k) of the Public Health Service Act, the pharmacology and toxicology information can be submitted as study reports in PDF format, without providing additional electronic, individual animal data listings?

FDA Response:

You may submit the data in the PDF format; however, all data including individual animal data should be submitted to the BLA.

Discussion:

The sponsor presented the attached slide presentation. The sponsor presented slide 36 in relation to the FDA response to Question 10.

Sandoz asked for clarification as to whether the individual animal data could be submitted in PDF format. The Agency confirmed that this was acceptable.

2.4 Clinical

Question 11:

Does the Agency agree that the clinical data package is sufficient to permit assessment of biosimilarity at the clinical level and the review of the respective sections of the proposed biosimilar BLA dossier?

FDA Response:

The proposed clinical package presented in the meeting package may not be adequate to support a demonstration of biosimilarity. We have the following concerns:

- **We note that study EP06-109 only compared a single 10 µg/kg SC dose PK of EP2006 with US-licensed Neupogen. For a PK similarity assessment for a G-CSF**

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

product, we strongly recommend that the selected dose (or doses) be in the linear ascending part of the dose-response curve (i.e., lower than 10 µg/kg which is on the plateau of the dose-response curve) and should be justified. In 2010, we recommended that you study both the 5 µg/kg and 10 µg/kg doses. As stated in the draft guidance for industry Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act (p. 7) –as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product. The draft guidance for industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product also explains that when the administered dose is on the plateau of a dose-response curve, the clinical trial will not be sensitive in detecting differences between the two products (see lines 749-750).

- With regard to study EP06-109, for PD sampling for CD34+ in peripheral blood to be adequate, you should characterize the AUC of CD34+ and CD34max following at least five daily doses. If the CD34+ data to support the mobilization indication is limited to single dose evaluation as is described in the meeting packet, you should provide a justification supporting the adequacy of the data in the BLA submission.
- As described in the draft guidance for industry on Biosimilars -- Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, a sponsor may seek to use data derived from clinical studies comparing a proposed product with a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act. In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. The type of bridging data needed to provide adequate scientific justification for this approach would likely include a clinical PK and/or PD study conducted with the U.S. licensed reference product. The adequacy of this scientific justification and bridge to the US-licensed reference product would be a review issue. In addition, a sponsor may submit publicly available information regarding the non-U.S.-licensed product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.

We note that a 3-way clinical PK and/or PD bridging study has not been conducted for this development program. Therefore, based on the information contained in the meeting package, we assume that you intend to scientifically justify the relevance of the comparative data obtained using the EU-approved filgrastim product to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge. As outlined in the response to Question 4, we note that the analytical data you intend to submit may not be sufficient to build an adequate scientific bridge. The analytical

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

bridge should include direct physicochemical comparison of all 3 products, US-licensed Neupogen to EP2006, the EU-approved filgrastim product to EP2006, and the EU-approved filgrastim product to US-licensed Neupogen, and all three comparisons should meet the pre-specified acceptance criteria for analytical similarity.

Assuming you intend to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge, you will need to provide a justification in your BLA as to the adequacy of the “analytical-only bridge” and why a 3-way clinical PK/PD comparison is not necessary to bridge data from your four PK/PD studies that utilized EU-approved filgrastim as the comparator. The absence of a 3-way bridging PK/PD study will be a review issue. However, if you cannot build an adequate scientific bridge to your four PK/PD studies that utilized EU-approved filgrastim as the comparator, based on the issues described in the first 2 bullets of the response to Question 11, the clinical data generated in study EP06-109 may not be sufficient to support a demonstration of biosimilarity of EP2006 to US-licensed Neupogen.

Based on the concerns identified regarding the adequacy of the analytical data to build a sufficient scientific bridge, we strongly encourage you to complete a single dose, three-way clinical PK bridging study, using an appropriate dose level, comparing US-licensed Neupogen, EU-approved filgrastim, and EP2006.

We note that the utility of data from the single arm study (EP06-301) in patients with breast cancer is limited due to the reliance on a historical control.

Discussion:

The sponsor presented the attached slide presentation. The sponsor presented slides 39-41 in relation to the FDA response to Question 11.

Sandoz stated their position that the 10 µg/kg dose falls in the linear portion of the dose-response curve. The FDA noted that PK/PD data from doses higher than 10 µg/kg would be needed to conclude that the 10 µg/kg dose falls in the linear portion of the dose-response curve. In addition, FDA noted that there is no difference in the PD response between the 5 µg/kg and 10 µg/kg doses.

The FDA emphasized the importance of establishing an adequate scientific bridge between EU-approved filgrastim and US-licensed Neupogen to justify the relevance of data obtained from the studies that used EU-approved filgrastim as a comparator.

The Sponsor stated that PK data are available on 54 evaluable patients from clinical study EP06-302 using US-licensed Neupogen and EP2006 at doses of 5 ug/kg. The FDA stated that analyses of these data would be important to support a demonstration of PK/PD similarity.

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

Also, see the summary of discussion regarding the scientific bridge captured under Question 4.

Question 12:

To address Pediatric Research Equity Act (PREA), Sandoz plans to submit a pediatric assessment consisting of scientific rationale and justification for extrapolation to treatment in pediatric patients. Since the underlying mechanism of action of the reference product Neupogen® is identical for all indications it is approved for, Sandoz considers it justified to extrapolate the clinical data from phase III studies and the biosimilarity of EP2006 demonstrated by totality of the overall package to all other remaining indications for which the reference product Neupogen® is approved for.

Does the Agency agree with this approach to address Pediatric Research Equity Act?

FDA Response:

Yes, we agree with your approach in principle. The adequacy of this approach will be a review issue. However, we note that your justification for extrapolation for purposes of demonstrating biosimilarity should focus on extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) in the context of your biosimilar development program rather than extrapolation of efficacy (but not safety or dosing) from adult populations to pediatric populations.

Discussion:

The sponsor presented the attached slide presentation. The sponsor presented slides 37-38 in relation to the FDA response to Question 12.

FDA noted that the approach presented by the sponsor in the slide presentation would need to be discussed internally, and that FDA would provide comments in a post-meeting note.

Post Meeting Note: *You asked if it would be acceptable to submit your proposed 351(k) BLA with the agreed, but not confirmed, initial pediatric study plan (iPSP). We refer you to the draft guidance entitled “Guidance for Industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans” (July 2013), which explains that “[i]f a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted.” FDA cannot commit to spending less than 90 days to provide initial comments on your iPSP, or less than 30 days to confirm agreement with your agreed iPSP. However, it should be noted that you may opt to spend less than 90 days for review of our comments on your iPSP and submission of your agreed iPSP. You should submit an agreed and confirmed initial pediatric study plan with your BLA submission.*

Question 13: Day-120 safety update

Sandoz will provide the interim safety reports of the European post-approval studies EP06- 401, EP06-402, and EP06-501 during the day-120 safety update if not included in the initial

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

application. Further, if new safety findings regarding the widely used product class of filgrastim-containing drugs are available for Sandoz, either from public available source or Sandoz data, it will be reported.

Does FDA agree with this proposal?

FDA Response:

Yes, we agree.

Discussion:

No discussion occurred.

Question 14: Format of study data/analysis programs

Data analyses were performed using SAS® Software. Sandoz intends to provide the Agency with all collected/derived data in CDISC SDTM-format, along with annotated CRFs (please find a sample CRF in Appendix 3 – Case Report Form), and a document including data set descriptions as well as variable descriptions (define.pdf). Data will be provided as SAS transport files (XPT files). All analyses of Sandoz will be built on the provided SDTMs.

Since the studies were originally analyzed based on non-CDISC data, the original SAS programs do not relate to the datasets submitted. Therefore, Sandoz does not intend to provide any SAS programs at the time of filing. The adaptation and validation of these programs is ongoing and specific programs will be provided upon request.

Does the Agency concur with Sandoz' that the data format and the potential to provide SAS programs upon request, is adequate to support the submission, filing, and review of Sandoz' proposed biosimilar BLA for EP2006?

FDA Response:

- **We concur with your data format.**
- **Please provide a Statistical Analysis Dataset, in SAS transport format to our Electronic Document Room (EDR). This dataset shall have one record only per subject and need to include at least following information:**
 - **Demographic variables**
 - **Baseline characteristics**
 - **Population flags**
 - **Efficacy outcomes (primary, secondary, etc.)**
 - **Covariates and subgroup variables**
 - **Subject disposition variables**
- **The define.pdf file should contain the descriptions of variable names on data sets. All derived variables should be clearly defined so that these variables can be traced to variables in the raw datasets. Please also include the programs that were used to derive the dataset.**

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

Discussion:

No discussion occurred.

Question 15: Data to be included and summarized

The clinical overview (Section 2.5) and the summaries (2.7.3 and 2.7.4) in Module 2 of the dossier will primarily be based on the results of five phase 1 studies (EP06-101, EP06-102, EP06-103, EP06-105, and EP06-109) conducted in healthy volunteers and one single-arm phase 3 (EP06-301) study in breast cancer patients. In addition, efficacy and safety results of the comparative Phase 3 trial (EP06-302) in breast cancer patients using vials and interim efficacy and safety data of study EP06-501 in healthy donors will be included as supportive data.

Due to the differences in the application route, frequency, and dose, Sandoz proposes to present the phase 1 study results side-by-side without any integrated analyses.

Based on the completely different setting in the phase 3 study as compared to the healthy volunteer studies and to the stem cell mobilization study and given that the supportive study EP06-302 uses a different presentation, no pooled analyses will be performed across these studies. In particular, Sandoz proposes not to include specific ISE and ISS documents in the file, but to assess and discuss the overall efficacy and safety profile in the clinical summary sections.

The four phase 1 studies conducted in Japan are considered only supportive and the results will not be included in the Module 2, however the study reports will be provided in Section 5.3 of the dossier.

Does the Agency concur with this approach?

FDA Response:

Yes, we agree.

As noted in the response to Question 7, in the event the data from the studies conducted in Japan are necessary to support your 351(k) application, sufficient data should be provided to establish the relationship between the material used in the studies and the EP2006 product for which you seek approval.

Discussion:

No discussion occurred.

2.5 Labeling

Question 16:

Does the Agency agree that the biosimilar prescribing information for EP2006 should be essentially the same as the prescribing information of the US reference listed biologic Neupogen®?

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

FDA Response:

Your proposed approach to draft proposed labeling is a reasonable starting point for submission of your proposed 351(k) BLA. Submit your draft proposed labeling for EP2006 in the PLR format. We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your 351(k) BLA.

Discussion:

No discussion occurred.

2.6 Additional Comments

Statistics

The proposed no imputation for missing data is not acceptable. Sensitivity analyses, including an appropriate method of imputation, should be performed to account for the limitation of the data and to examine the potential impact of any missing data. Too much missing data undermine the reliability and confidence of the results. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.

Discussion:

No discussion occurred.

Product Quality Microbiology

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful (b) (4) hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- (b) (4)
- Bioburden and endotoxin data obtained (b) (4) of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products



The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- (b) (4) retention study (b) (4)
- (b) (4)
- (b) (4) Hold times should be validated at manufacturing scale.
- (b) (4)
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Shipping validation studies.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed (b) (4) for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed (b) (4) as appropriate (3.2.P.5).
- Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610(b).

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

- The effect of hold time on endotoxin recovery should be assessed

Discussion:

No discussion occurred.

Immunogenicity

Table 13-1 does not specify the location of the validation reports for immunogenicity assays used to evaluate human sera samples and the immunogenicity data. Provide validation reports for immunogenicity assays in section 5.3.1. "Reports of Biopharmaceutical Studies" under 5.3.1.4 "Reports of Bioanalytical Methods for Human Studies". The immunogenicity data should be included under Section 2.7. "Clinical Summary" and a synopsis in section 2.5. "Clinical Overview".

Discussion:

No discussion occurred.

Regulatory

1. You describe the strength of your proposed product and the reference product in your Briefing Book as 30 MU/0.5mL and 48 MU/0.8 mL for the prefilled syringe. It is unclear why you have chosen different units of measure ("MU" or "Mio. Units") than appear in the approved product labeling for US-licensed Neupogen, the reference product, which describes the strength of the product in mcg/mL. As stated in FDA's draft guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the BPCI Act, the total content of drug substance and concentration of drug substance generally should be expressed using the same measure as the reference product (see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm259809.htm#Q12>). Revise all references to the strength of your proposed product and the reference product accordingly.
2. You state that the applicant will provide a "reviewer's guide" as appendix to the cover letter with the initial submission containing information on, among other things, naming conventions. Please note that your 351(k) BLA submission should clearly describe whether the comparator used in each study is the US-licensed reference product or a non-U.S.-licensed comparator product, and use consistent nomenclature throughout your 351(k) BLA submission that clearly differentiates these products. A single explanation in the reviewer's guide will not be adequate. Furthermore, we note that statements such as "Using Neupogen as reference product at every stage in development..." (Briefing Book, page 16) are misleading and erroneous, and require correction.

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

Discussion:

No discussion occurred.

Additional Discussion:

- *The sponsor noted their plan to submit the 351(k) BLA for EP2006 requesting licensure as a biosimilar to US-licensed Neupogen in May 2014.*
- *The sponsor noted their intention to request a meeting to discuss an interchangeability designation for EP2006 after the original BLA to support a demonstration of biosimilarity is submitted.*

3.0 PREA PEDIATRIC STUDY PLAN

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(n) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to the submission of your planned 351(k) BLA; see additional comments below regarding expected review timelines.

Section 506 of the Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 505B(e) of the FD&C Act to set forth a process for reaching agreement between applicants and FDA on initial PSPs. This provision of FDASIA has an effective date of January 5, 2013. Section 505B(e)(2)(A) of the FD&C Act as amended by FDASIA provides that applicants should submit an initial PSP no later than 60 calendar days after the date of the end-of-Phase 2 meeting, or at another time agreed upon by FDA and the applicant. As required by FDASIA, FDA has issued guidance on PSP requirements, including timing of PSP submission. Refer to Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>

IND 109197
Meeting Minutes
November 19, 2013

Office of Hematology and Oncology Products
Division of Hematology Products

Sections 505B(e)(2)(C) and 505B(e)(3) set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

5.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

6.0 ACTION ITEMS

None.

7.0 ATTACHMENTS AND HANDOUTS

A copy of slides presented at the meeting is attached.

41 Pages have been Withheld in Full as B4(CCI/TS) Immediately
Following this Page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
12/19/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 109197

MEETING PRELIMINARY COMMENTS

Sandoz Inc.
Attention: John M. Pakulski
Head Regulatory Affairs
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Pre-Investigational New Drug Application (PIND) file for EP2006.

We also refer to your August 20, 2013, correspondence, received August 22, 2013, requesting a meeting to discuss and secure FDA's guidance and agreement on the format of the content of the planned BLA in order to support the licensure of Sandoz' rhG-CSF product under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hard copy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Monsurat Lara Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: November 19, 2013; 10:00 AM – 11:00 AM EDT
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: PIND 109197
Product Name: EP2006 (proposed biosimilar to US-licensed Neupogen)
Indication: EP2006 is being developed for the same indications as approved for US-licensed Neupogen
Sponsor/Applicant Name: Sandoz Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 19, 2013; 10:00 AM – 11:00 AM EDT between Sandoz and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On August 22, 2013, the Agency received a meeting request from Sandoz to discuss and secure FDA's guidance and agreement on the format of the content of the planned BLA in order to support the licensure of Sandoz' rhG-CSF product under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)). The Agency granted the meeting request on September 7, 2013, as a Biosimilar Biological Product Development (BPD) Type 4 Meeting.

On November 14, 2013, the Division emailed Sandoz the preliminary responses to the questions contained in the meeting information package received August 22, 2013.

PIND 109197
Preliminary Meeting Comments

2. DISCUSSION

General Introductory Comments:

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Sandoz and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

Please note that for ease of reference and discussion, we have renumbered your questions in sequential order.

2.1 Electronic submission – eCTD

Sandoz intends to submit the initial application in electronic form using the eCTD format according to current FDA requirements. In the following the applicant would like to take the chance to point out Sandoz' position and strategy on eCTD.

The applicant will provide a "reviewer's guide" as appendix to the cover letter with the initial submission containing information on the content, hyperlinking strategy, naming conventions, legacy documents, literature references, metadata etc., in order to facilitate a smooth and convenient review of the application for the Agency.

Because Sandoz pursues a global development, it proposes to provide all documentation in A4 format while guaranteeing that the page layout is compatible with letter format. In other words, all documents will be suitable for printing on letter format paper as well as A4 format paper. Page margins follow the specifications in the guideline (PDF Portable Document Format (PDF) Specifications).

Question 1:

Annotated table of contents

Sandoz intends to submit an electronic CTD dossier as required by the FDA. In the briefing package submitted together with this meeting request, a table of contents of the dossier is provided as Table 13-1. A brief description of all documents is included into this table of contents.

Does the Agency agree that the proposed documents as described are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required, which have to be included in the eCTD dossier for an application under section 351(k) of the Public Health Service Act?

PIND 109197
Preliminary Meeting Comments

FDA Response:

No, we do not agree that your proposal is adequate. Please see the responses to the remaining questions for information on additional documents and information that should be included in your planned eCTD submission.

Question 2:

Scanned PDFs – OCR

Some existing documents such as literature references or CRF's are not available in a searchable format (i.e. not created from a readable source or OCR).

Does the Agency agree that it is acceptable to include these documents in the biosimilar BLA submission as "non-searchable" PDF documents?

FDA Response:

Yes, we agree.

Question 3:

Hyperlinking

Sandoz intends to use efficient inter-document hyperlinking between individual dossier documents, besides adequate intra-document hyperlinking. This will facilitate a quick and convenient review. Hyperlinking is planned within Modules 2 and 3 and from Module 2 to the respective sections in Modules 3, 4, and 5. It is not planned to hyperlink documents within Modules 4 and 5 or across Modules 3, 4 and 5 to keep the number of hyperlinks to a reasonable amount.

Does the Agency agree with the proposed hyperlinking strategy?

FDA Response:

No, we do not agree. Please provide hyperlinks within Module 5.

2.1 CMC

Question 4:

Does the Agency agree that the CMC data package is sufficient to permit review of the registration application?

FDA Response:

No, we do not agree. We have insufficient information to determine if the CMC data package is sufficient to permit meaningful review of the BLA. Furthermore, you stated that you intend to include "only selected information of the data packages" in the CTD (page 27). We advise that the CMC data and information expected for review of the proposed biosimilar product should be included in the BLA.

PIND 109197
Preliminary Meeting Comments

Based on the limited CMC information you have provided, we have identified the following issues:

- 1. The “final” analytical similarity assessment strategy, as outlined in the response to our information request dated November 1, 2013, intended to demonstrate that EP2006 is analytically “highly similar” to the reference product, US-licensed Neupogen, and to support an analytical bridge between EP2006, US-licensed Neupogen and the EU-approved filgrastim product (marketed in the EU as “Neupogen”) is based on limited data. We have identified deficiencies including limited product characterization (e.g. lack of tests to evaluate product strength and disulfide bond integrity, and insufficient orthogonal methods for characterization of aggregates and higher order structure) and limited number of lots of EP2006, US-licensed Neupogen and the EU-approved filgrastim product analyzed. We note that the data may not be sufficient to support a demonstration of “highly similar” or to build an adequate scientific bridge.**

In your response to the information request, you state that you “compare your biosimilar products to the reference product throughout the development process on many more lots over time”. The comparative analytical data generated during development may be considered to support analytical similarity provided the analytical characterization of the products is robust, sufficient lots of EP2006, US-licensed Neupogen and the EU-approved filgrastim product were evaluated, and the EP2006 material used in the assessment includes EP2006 product manufactured by the clinical process and by the proposed commercial process for which you seek approval.

- 2. We note that you have made changes to the manufacture of EP2006 drug substance and drug product (e.g. scale and site of manufacture), and plan to submit comparability data in your BLA submission. Please be aware that in addition to demonstrating comparability between the pre-change and post-change drug substance (DS) and drug product (DP), analytical similarity of EP2006 manufactured by the clinical processes (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at Lek Pharmaceuticals d.d., Slovenia and IDT Biologika GmbH, Germany) and proposed commercial product (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at GP Grenzach Produktions GmbH, Germany) needs to be demonstrated to US-licensed Neupogen.**
- 3. You plan to submit analytical data comparing EP2006, US-licensed Neupogen and the EU-approved filgrastim product to demonstrate analytical similarity of your product to the reference product, US-licensed Neupogen, and to establish an analytical bridge between EP2006, US-licensed Neupogen, and the EU-approved filgrastim product. In your BLA submission, clearly specify the data you intend to use to demonstrate analytical similarity and the data intended to establish the analytical bridge between your product, the reference product, and the EU-approved filgrastim product. For the analytical bridge, we expect all three comparisons (EP2006 to US-licensed Neupogen, EP2006 to the EU-approved filgrastim product, and the EU-approved filgrastim product to US-approved Neupogen) to meet the pre-specified acceptance criteria for similarity. Additionally, specify whether the analytical similarity assessment was**

PIND 109197
Preliminary Meeting Comments

conducted with EP2006 lots manufactured by the clinical and proposed commercial processes.

With respect to organization of the CMC data package, address the following in the BLA submission:

1. Module 3 should also include the following data:

- i. You propose to provide “Executed Batch Records” upon request. This is not acceptable. Executed batch records should be provided in the BLA submission.**
- ii. You plan to provide analytical method validation reports for non-compendial methods in Module 3 section 3.2.S.4.3. These reports along with method validation protocols should be located in the regional section (3.2.R)**
- iii. Table 13-1 does not specify whether analytical comparability and analytical similarity protocols will be provided. Provide analytical comparability and analytical similarity protocols in separate 3.2.R modules.**
- iv. Functional assays, including mechanism of action, should be provided and a justification that EP2006 has the same mechanism(s) of action as US-licensed Neupogen needs to be included in your BLA submission. Provide a summary of the data under Module 2.6 (“Nonclinical Written and Tabulated Summaries”) and Module 2.3 (“Quality Overall Summary”) with a link to the relevant section(s) of Module 3.**

2. In addition, include the following additional information in the relevant CTD sections.

CTD section	Comment
1.1.2 FDA form 356h	Indicate if the manufacturing and testing sites are ready for inspection.
1.3 Administrative information	A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections. Environmental Assessment or a request for categorical exclusion
2 Common Technical document summaries	Summaries of “Executed Batch Records” and summaries of “Analytical Comparability and Analytical Similarity protocols”
3.2.S.2.5 Process validation and/or evaluation	<ul style="list-style-type: none"> Three successful consecutive (b) (4) hold time validation runs at manufacturing scale from microbiology perspective.

PIND 109197
Preliminary Meeting Comments

	<ul style="list-style-type: none"> • Information (b) (4) including microbiology data • Data summaries of shipping validation studies
3.2.S.4.3 Validation of analytical procedures	Qualification reports for bioburden and endotoxin tests.
3.2.P.3.5 Process validation and/or evaluation	<ul style="list-style-type: none"> • (b) (4) retention study report (b) (4) <p>(b) (4)</p> <ul style="list-style-type: none"> • Hold time validation at scale from microbiology perspective <p>(b) (4)</p> <ul style="list-style-type: none"> • Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs, • A description of the routine environmental monitoring program • Shipping validation data, including container closure integrity data
3.2.P.5.3 Validation of analytical procedures	Qualification of bioburden, endotoxin, and sterility tests. Results of rabbit pyrogen test using three drug product lots.
3.2.P.8.2 Post-approval Stability Protocol and Commitment	Container closure integrity test (b) (4) (b) (4) on the stability program.
3.2.A Appendices	Information about other products manufactured in the facilities and strategies to prevent contamination and cross-contamination should also be described in this section.

PIND 109197
Preliminary Meeting Comments

Question 5:

Does the Agency concur with Sandoz' proposal to provide the detailed summary reports for biosimilarity studies with the originators as well as the comparability studies performed for quality changes during development as separate 3.2.R modules?

FDA Response:

Your proposal to provide analytical similarity reports and analytical comparability reports as separate 3.2.R. modules is acceptable. However, full analytical similarity, and analytical comparability reports should be provided. Please refer to comment 3 in the response to question 1 above regarding the content of the analytical similarity and analytical bridge data.

Question 6:

Does the Agency concur with Sandoz' proposal to include more detailed information on the process characterization as separate 3.2.R module(s) (e.g. detailed description of methodology and specific examples from process characterization studies)?

FDA Response:

Yes, we concur.

Question 7:

Sandoz will provide information on several supportive clinical studies (see also Clinical Question 5). These studies were conducted using (b) (4) which is different from the product Sandoz is seeking approval for (b) (4)

Does the Agency agree with Sandoz's proposal that inclusion of CMC data on (b) (4) used in supportive clinical studies is not needed?

FDA Response:

No, we do not concur. The purpose of the "supportive clinical studies" is not clear from the information provided in your meeting package. Therefore, it is unclear whether the associated CMC data are required in the BLA. In the event the "supportive clinical data" generated with the different (b) (4) material are required to support your 351(k) application, sufficient CMC data should be provided to establish the relationship between such (b) (4) material and the EP2006 product for which you seek approval.

Question 8:

The product concerned is considered a combination product composed of the drug and two device components, in particular a pre-filled syringe and a needle safety guard (b) (4). Sandoz proposes to submit information on the pre-filled syringe and the needle safety guard, and their respective interfaces in a summary document in section 3.2.R of the eCTD. To avoid redundant information, appropriate hyperlinks to Module 3.2.P documents will be set and the respective information will not be repeated in Module 3.2.R. As requested during the pre-IND

PIND 109197
Preliminary Meeting Comments

meeting (see pre-IND meeting minutes dated 28 October 2010), Sandoz will provide objective evidence that the device components can be handled safely and effectively by the intended user groups consisting of patients, healthcare professionals, and caregivers. The summary report that Sandoz intends to provide is based on a simulated use handling study conducted by Novartis Pharma AG for a combination product composed of the identical device components (i.e. pre-filled syringe, needle safety guard) and comparable instructions for use regarding the Novartis product. This study revealed that all intended user groups can safely and effectively handle the device. Although the patient population differs between the Novartis product and EP2006 it can be safely assumed that the device components also suits EP2006 users, because they don't have any special needs from a human factors perspective that is caused by the disease (e.g. such as patients suffering from rheumatoid arthritis (RA)).

Does the Agency concur that the outlined approach to address the requirements for the presented combination product EP2006 is acceptable?

FDA Response:

You stated that that you will provide a summary from a simulated use study that was conducted with a Novartis product. In addition, you stated that the device components (pre-filled syringe and needle safety guard) are identical to the Novartis product. However, it appears that the patient population differs between the Novartis product and EP2006. Different patient population indicates different intended user group. A key component of human factors/usability validation testing is that users who are representative of actual users be used for the testing.

At this time, we cannot determine whether your approach is acceptable without information that provides a comprehensive analysis of the intended users for your product and how they are comparable to the users of the Novartis product, and without a comprehensive use-related risks analysis on the use of your product. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

You should submit these detailed analyses for review. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

PIND 109197
Preliminary Meeting Comments

2.3 Pharmacology/Toxicology

Question 9:

Does the Agency agree that the pharmacology and toxicology package summarized in Table 12-1 is sufficient to permit assessment of biosimilarity at the nonclinical level and the review of the respective sections of proposed biosimilar BLA dossier?

FDA Response:

Yes. The pharmacology and toxicology package is acceptable for BLA filing. However, a final determination of biosimilarity will be made during the BLA review based on the totality of the evidence submitted.

Question 10:

Does the Agency agree that for licensure of EP2006 as a biosimilar product to Neupogen under 351(k) of the Public Health Service Act, the pharmacology and toxicology information can be submitted as study reports in PDF format, without providing additional electronic, individual animal data listings?

FDA Response:

You may submit the data in the PDF format; however, all data including individual animal data should be submitted to the BLA.

2.4 Clinical

Question 11:

Does the Agency agree that the clinical data package is sufficient to permit assessment of biosimilarity at the clinical level and the review of the respective sections of the proposed biosimilar BLA dossier?

FDA Response:

The proposed clinical package presented in the meeting package may not be adequate to support a demonstration of biosimilarity. We have the following concerns:

- We note that study EP06-109 only compared a single 10 µg/kg SC dose PK of EP2006 with US-licensed Neupogen. For a PK similarity assessment for a G-CSF product, we strongly recommend that the selected dose (or doses) be in the linear ascending part of the dose-response curve (i.e., lower than 10 µg/kg which is on the plateau of the dose-response curve) and should be justified. In 2010, we recommended that you study both the 5 µg/kg and 10 µg/kg doses. As stated in the draft guidance for industry Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act (p. 7) –as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of**

PIND 109197
Preliminary Meeting Comments

the proposed biosimilar product directly with the U.S.-licensed reference product. The draft guidance for industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product also explains that when the administered dose is on the plateau of a dose-response curve, the clinical trial will not be sensitive in detecting differences between the two products (see lines 749-750).

- With regard to study EP06-109, for PD sampling for CD34+ in peripheral blood to be adequate, you should characterize the AUC of CD34+ and CD34max following at least five daily doses. If the CD34+ data to support the mobilization indication is limited to single dose evaluation as is described in the meeting packet, you should provide a justification supporting the adequacy of the data in the BLA submission.**
- As described in the draft guidance for industry on Biosimilars — Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, a sponsor may seek to use data derived from clinical studies comparing a proposed product with a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act. In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. The type of bridging data needed to provide adequate scientific justification for this approach would likely include a clinical PK and/or PD study conducted with the U.S. licensed reference product. The adequacy of this scientific justification and bridge to the US-licensed reference product would be a review issue. In addition, a sponsor may submit publicly available information regarding the non-U.S.-licensed product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.**

We note that a 3-way clinical PK and/or PD bridging study has not been conducted for this development program. Therefore, based on the information contained in the meeting package, we assume that you intend to scientifically justify the relevance of the comparative data obtained using the EU-approved filgrastim product to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge. As outlined in the response to Question 4, we note that the analytical data you intend to submit may not be sufficient to build an adequate scientific bridge. The analytical bridge should include direct physicochemical comparison of all 3 products, US-licensed Neupogen to EP2006, the EU-approved filgrastim product to EP2006, and the EU-approved filgrastim product to US-licensed Neupogen, and all three comparisons should meet the pre-specified acceptance criteria for analytical similarity.

Assuming you intend to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge, you will need to provide a justification in your BLA as to the adequacy of the “analytical-only bridge” and why a 3-way clinical PK/PD comparison is not necessary to bridge data from your four PK/PD

PIND 109197
Preliminary Meeting Comments

studies that utilized EU-approved filgrastim as the comparator. The absence of a 3-way bridging PK/PD study will be a review issue. However, if you cannot build an adequate scientific bridge to your four PK/PD studies that utilized EU-approved filgrastim as the comparator, based on the issues described in the first 2 bullets of the response to Question 11, the clinical data generated in study EP06-109 may not be sufficient to support a demonstration of biosimilarity of EP2006 to US-licensed Neupogen.

Based on the concerns identified regarding the adequacy of the analytical data to build a sufficient scientific bridge, we strongly encourage you to complete a single dose, three-way clinical PK bridging study, using an appropriate dose level, comparing US-licensed Neupogen, EU-approved filgrastim, and EP2006.

We note that the utility of data from the single arm study (EP06-301) in patients with breast cancer is limited due to the reliance on a historical control.

Question 12:

To address Pediatric Research Equity Act (PREA), Sandoz plans to submit a pediatric assessment consisting of scientific rationale and justification for extrapolation to treatment in pediatric patients. Since the underlying mechanism of action of the reference product Neupogen® is identical for all indications it is approved for, Sandoz considers it justified to extrapolate the clinical data from phase III studies and the biosimilarity of EP2006 demonstrated by totality of the overall package to all other remaining indications for which the reference product Neupogen® is approved for.

Does the Agency agree with this approach to address Pediatric Research Equity Act?

FDA Response:

Yes, we agree with your approach in principle. The adequacy of this approach will be a review issue. However, we note that your justification for extrapolation for purposes of demonstrating biosimilarity should focus on extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) in the context of your biosimilar development program rather than extrapolation of efficacy (but not safety or dosing) from adult populations to pediatric populations.

Question 13: Day-120 safety update

Sandoz will provide the interim safety reports of the European post-approval studies EP06-401, EP06-402, and EP06-501 during the day-120 safety update if not included in the initial application. Further, if new safety findings regarding the widely used product class of filgrastim-containing drugs are available for Sandoz, either from public available source or Sandoz data, it will be reported.

Does FDA agree with this proposal?

PIND 109197
Preliminary Meeting Comments

FDA Response:

Yes, we agree.

Question 14: Format of study data/analysis programs

Data analyses were performed using SAS® Software. Sandoz intends to provide the Agency with all collected/derived data in CDISC SDTM-format, along with annotated CRFs (please find a sample CRF in Appendix 3 – Case Report Form), and a document including data set descriptions as well as variable descriptions (define.pdf). Data will be provided as SAS transport files (XPT files). All analyses of Sandoz will be built on the provided SDTMs.

Since the studies were originally analyzed based on non-CDISC data, the original SAS programs do not relate to the datasets submitted. Therefore, Sandoz does not intend to provide any SAS programs at the time of filing. The adaptation and validation of these programs is ongoing and specific programs will be provided upon request.

Does the Agency concur with Sandoz' that the data format and the potential to provide SAS programs upon request, is adequate to support the submission, filing, and review of Sandoz' proposed biosimilar BLA for EP2006?

FDA Response:

- **We concur with your data format.**
- **Please provide a Statistical Analysis Dataset, in SAS transport format to our Electronic Document Room (EDR). This dataset shall have one record only per subject and need to include at least following information:**
 - **Demographic variables**
 - **Baseline characteristics**
 - **Population flags**
 - **Efficacy outcomes (primary, secondary, etc.)**
 - **Covariates and subgroup variables**
 - **Subject disposition variables**
- **The define.pdf file should contain the descriptions of variable names on data sets. All derived variables should be clearly defined so that these variables can be traced to variables in the raw datasets. Please also include the programs that were used to derive the dataset.**

Question 15: Data to be included and summarized

The clinical overview (Section 2.5) and the summaries (2.7.3 and 2.7.4) in Module 2 of the dossier will primarily be based on the results of five phase 1 studies (EP06-101, EP06-102, EP06-103, EP06-105, and EP06-109) conducted in healthy volunteers and one single-arm phase 3 (EP06-301) study in breast cancer patients. In addition, efficacy and safety results of the comparative Phase 3 trial (EP06-302) in breast cancer patients using vials and interim efficacy and safety data of study EP06-501 in healthy donors will be included as supportive data.

Due to the differences in the application route, frequency, and dose, Sandoz proposes to present the phase 1 study results side-by-side without any integrated analyses.

PIND 109197
Preliminary Meeting Comments

Based on the completely different setting in the phase 3 study as compared to the healthy volunteer studies and to the stem cell mobilization study and given that the supportive study EP06-302 uses a different presentation, no pooled analyses will be performed across these studies. In particular, Sandoz proposes not to include specific ISE and ISS documents in the file, but to assess and discuss the overall efficacy and safety profile in the clinical summary sections.

The four phase 1 studies conducted in Japan are considered only supportive and the results will not be included in the Module 2, however the study reports will be provided in Section 5.3 of the dossier.

Does the Agency concur with this approach?

FDA Response:

Yes, we agree.

As noted in the response to Question 7, in the event the data from the studies conducted in Japan are necessary to support your 351(k) application, sufficient data should be provided to establish the relationship between the material used in the studies and the EP2006 product for which you seek approval.

2.5 Labeling

Question 16:

Does the Agency agree that the biosimilar prescribing information for EP2006 should be essentially the same as the prescribing information of the US reference listed biologic Neupogen®?

FDA Response:

Your proposed approach to draft proposed labeling is a reasonable starting point for submission of your proposed 351(k) BLA. Submit your draft proposed labeling for EP2006 in the PLR format. We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your 351(k) BLA.

2.6 Additional Comments

Statistics

The proposed no imputation for missing data is not acceptable. Sensitivity analyses, including an appropriate method of imputation, should be performed to account for the limitation of the data and to examine the potential impact of any missing data. Too much missing data undermine the reliability and confidence of the results. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.

PIND 109197
Preliminary Meeting Comments

Product Quality Microbiology

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful (b) (4) hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- (b) (4)
- Bioburden and endotoxin data obtained (b) (4) of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- (b) (4)

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- (b) (4) retention study (b) (4)
- (b) (4)
- (b) (4). Hold times should be validated at manufacturing scale.
- (b) (4)

PIND 109197

Preliminary Meeting Comments

- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Shipping validation studies.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed (b) (4) for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed (b) (4), as appropriate (3.2.P.5).
- Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610(b).
- The effect of hold time on endotoxin recovery should be assessed (b) (4)

Immunogenicity

Table 13-1 does not specify the location of the validation reports for immunogenicity assays used to evaluate human sera samples and the immunogenicity data. Provide validation reports for immunogenicity assays in section 5.3.1, "Reports of Biopharmaceutical Studies" under 5.3.1.4 "Reports of Bioanalytical Methods for Human Studies". The immunogenicity data should be included under Section 2.7, "Clinical Summary" and a synopsis in section 2.5, "Clinical Overview".

Regulatory

1. You describe the strength of your proposed product and the reference product in your Briefing Book as 30 MU/0.5mL and 48 MU/0.8 mL for the prefilled syringe. It is unclear why you have chosen different units of measure ("MU" or "Mio. Units") than appear in the approved product labeling for US-licensed Neupogen, the reference product, which describes the strength of the product in mcg/mL. As stated in FDA's draft guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the BPCI Act, the total content of drug substance and concentration of drug substance generally should be expressed using the same measure as the reference product (see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm2598>

PIND 109197
Preliminary Meeting Comments

[09.htm#Q12](#)). Revise all references to the strength of your proposed product and the reference product accordingly.

2. You state that the applicant will provide a “reviewer’s guide” as appendix to the cover letter with the initial submission containing information on, among other things, naming conventions. Please note that your 351(k) BLA submission should clearly describe whether the comparator used in each study is the US-licensed reference product or a non-U.S.-licensed comparator product, and use consistent nomenclature throughout your 351(k) BLA submission that clearly differentiates these products. A single explanation in the reviewer’s guide will not be adequate. Furthermore, we note that statements such as “Using Neupogen as reference product at every stage in development...” (Briefing Book, page 16) are misleading and erroneous, and require correction.

3.0 PREA PEDIATRIC STUDY PLAN

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(n) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to the submission of your planned 351(k) BLA; see additional comments below regarding expected review timelines.

Section 506 of the Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 505B(e) of the FD&C Act to set forth a process for reaching agreement between applicants and FDA on initial PSPs. This provision of FDASIA has an effective date of January 5, 2013. Section 505B(e)(2)(A) of the FD&C Act as amended by FDASIA provides that applicants should submit an initial PSP no later than 60 calendar days after the date of the end-of-Phase 2 meeting, or at another time agreed upon by FDA and the applicant. As required by FDASIA, FDA has issued guidance on PSP requirements, including timing of PSP submission. Refer to Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>

PIND 109197
Preliminary Meeting Comments

Sections 505B(e)(2)(C) and 505B(e)(3) set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
11/14/2013

EXHIBIT 12

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761042Orig1s000

Trade Name: Erelzi Injection 25 mg/0.5 mL and 50 mg/mL

Generic or Proper Name: etanercept-szzs

Sponsor: Sandoz Inc.

Approval Date: August 30, 2016

Indications: Erelzi is indicated for:

- Rheumatoid arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO) in adults

CENTER FOR DRUG EVALUATION AND RESEARCH

761042Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	X
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761042Orig1s000

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761042

BLA APPROVAL

Sandoz Inc.
100 College Road West
Princeton, NJ 08540

Attention: Zhengyu (Eddy) Liu, PhD
Manager, Regulatory Affairs

Dear Dr. Liu:

Please refer to your Biologics License Application (BLA) dated July 30, 2015, received July 30, 2015, and your amendments, submitted under section 351(k) of the Public Health Service Act for Erelzi (etanercept-szzs) Injection 25 mg/0.5 mL and 50 mg/mL.

We acknowledge receipt of your major amendment dated April 28, 2016, which extended the goal date by three months.

LICENSING

We have approved your BLA for Erelzi (etanercept-szzs) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Erelzi under your existing Department of Health and Human Services U.S. License No. 2003. Erelzi is indicated for

- Rheumatoid Arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO) in adults

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture etanercept-szzs drug substance at Sandoz GmbH in Langkampfen, Austria. The final formulated product will be manufactured, filled, labeled, and packaged at Novartis Pharma Stein AG, Stein, Switzerland. You may label your product with the proprietary name, Erelzi, and will market it in single-dose prefilled syringes containing 25 mg/0.5 mL or 50 mg/mL Injection and single-dose prefilled Sensoready Pens containing 50 mg/mL Injection.

BLA 761042
Page 2

DATING PERIOD

The dating period for Erelzi shall be 24 months from the date of manufacture when stored at 2-8°C followed by 28 days at 25±2°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Erelzi to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Erelzi, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

BLA 761042
Page 3

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved BLA 761042.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for the following indications:

- Psoriatic Arthritis because necessary studies are impossible or highly impracticable.
- Ankylosing Spondylitis because necessary studies are impossible or highly impracticable.
- Plaque Psoriasis because there is evidence strongly suggesting that the product would be unsafe in all pediatric age groups

We are waiving the pediatric study requirement for Polyarticular Juvenile Idiopathic Arthritis (pJIA) for ages 0 to 1 year 11 months because necessary studies are impossible or highly impracticable. This is because there are too few children with pJIA to study.

We are deferring submission of your pediatric study for pJIA for ages 2 to 17 years for this application because development of a pediatric presentation is not complete.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

BLA 761042
Page 4

- 3110-1 Develop a presentation that can be used to accurately administer etanercept-szss to pediatric patients who weigh less than 63 kg.

Final Report Submission: December 2019

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3110-2 Develop and implement an analytical method for release and stability testing of GP2015 drug substance and drug product that can adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants. Submit the method final validation report and the release and stability acceptance criteria as a Prior Approval Supplement.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2017

- 3110-3 Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (e.g., surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. Submit the final report as a Changes Being Effected in 30 days (CBE30) and include any change in filtration parameters based upon the study.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2017

- 3110-4 Use a validated method to measure break loose, glide force (BLGF) for (b) (4) drug product pre-filled syringes to generate data from commercial batches to define

BLA 761042
Page 5

release specifications for BLGF. Submit the study report and specifications for BLGF including testing site in the annual report.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2019

- 3110-5 Develop methods for confirming the injection depth (e.g. needle length exposed for injection), audible feedback (e.g. occurrence of second click) and visual feedback (e.g. plunger fills the window and stops moving) for release testing. Define release specifications that meet design output specifications for injection depth, audible feedback, and visual feedback for lot release testing prior to launch of Erelzi. Submit the study report and release specifications in the annual report.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2017

- 3110-6 Complete transport validation testing to assess mechanical stress on the new folding box and transport carton prior to launch of Erelzi. Submit the final transport validation report.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2016

Submit clinical protocols to your IND 114187 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70, you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

BLA 761042
Page 6

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

BLA 761042
Page 7

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
08/30/2016

EXHIBIT 13

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761071Orig1s000

Trade Name: Hyrimoz injection, 40 mg/0.8 mL

Generic or Proper Name: adalimumab-adaz

Sponsor: Sandoz Inc.

Approval Date: October 30, 2018

Indication: Hyrimoz is indicated for:

Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.

Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.

Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's Disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The

effectiveness of HYRIMOZ has not been established in patients who have lost response to or were intolerant to TNF-blockers.

Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

CENTER FOR DRUG EVALUATION AND RESEARCH

761071Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	X
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	X
Product Quality Review(s)	X
Non-Clinical Review(s)	X
Statistical Review(s)	X
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761071Orig1s000

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761071

BLA APPROVAL

Sandoz Inc.
100 College Road West
Princeton, NJ 08540

Attention: Bijal Pandhi, PharmD
Associate Director, Regulatory Strategy and Science

Dear Dr. Pandhi:

Please refer to your Biologics License Application (BLA) dated October 30, 2017, received October 30, 2017, and your amendments, submitted under section 351(k) of the Public Health Service Act for Hyrimoz (adalimumab-adaz) injection, 40 mg/0.8 mL for subcutaneous administration.

LICENSING

We have approved your BLA for Hyrimoz (adalimumab-adaz) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Hyrimoz under your existing Department of Health and Human Services U.S. License No. 2003. Hyrimoz is indicated for:

1. Rheumatoid Arthritis (RA):
 - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.
2. Juvenile Idiopathic Arthritis (JIA):
 - Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older.
3. Psoriatic Arthritis (PsA):
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis.
4. Ankylosing Spondylitis (AS):
 - Reducing signs and symptoms in adult patients with active ankylosing spondylitis.

BLA 761071
Page 2

5. Adult Crohn's Disease (adult CD):

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

6. Ulcerative Colitis (UC):

- Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP).

7. Plaque Psoriasis (PsO):

- The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture adalimumab-adaz drug substance at Sandoz GmbH Schaffhausen in Langkampfen, Austria, and (b) (4). The final formulated drug product will be manufactured, filled, and packaged at (b) (4), assembled, labeled, and packaged at (b) (4). You may label your product with the proprietary name, Hyrimoz, and will market it in 40 mg/0.8 mL injection, in a single-dose prefilled syringe or a single-dose autoinjector.

DATING PERIOD

The dating period for Hyrimoz shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Hyrimoz to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BLA 761071
Page 3

Any changes in the manufacturing, testing, packaging, or labeling of Hyrimoz, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Medication Guide, and Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761071.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an

BLA 761071
Page 4

assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The following comments pertain to Rheumatoid Arthritis indication:

We are waiving the pediatric studies requirement for the Polyarticular Juvenile Idiopathic Arthritis (pJIA) in pediatric patients 0 to less than 2 years of age because necessary studies are impossible or highly impracticable given that the disease is rarely diagnosed in this population.

We are deferring the required pediatric assessment for pediatric patients 2 years to less than 4 years of age. See Deferred Pediatric Assessments below.

We are deferring the required pediatric assessment for patients < 30 kg. See Deferred Pediatric Assessments below.

The following comment pertains to Psoriatic Arthritis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comment pertains to Ankylosing Spondylitis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comments pertain to Crohn's Disease indication:

We are waiving the pediatric study requirements for pediatric patients with Crohn's disease less than 6 years of age because necessary studies for this product are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

We are deferring the required pediatric assessment for pediatric patients 6 years to 17 years of age. See Deferred Pediatric Assessments below.

The following comments pertain to Ulcerative Colitis indication:

We are waiving the pediatric study requirements for pediatric patients with ulcerative colitis less than 5 years of age because necessary studies for this product are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

We are deferring the required pediatric assessment for pediatric patients 5 to 17 years of age. See Deferred Pediatric Assessments below.

BLA 761071
Page 5

The following comment pertains to Plaque Psoriasis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

Deferred Pediatric Assessments

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

3506-1 Assessment of Hyrimoz (adalimumab-adaz) for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 to less than 4 years of age

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date: September 2021

3506-2 Assessment of Hyrimoz (adalimumab-adaz) for the treatment of pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date: September 2021

3506-3 Assessment of Hyrimoz (adalimumab-adaz) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date: December 2020

3506-4 Develop a presentation that can be used to accurately administer Hyrimoz (adalimumab-adaz) to pediatric patients who weigh less than 30 kg

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date: September 2021

BLA 761071
Page 6

Submit the protocols to your IND 115732, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3506-5 To qualify the bioburden test method for the (b) (4) samples at Sandoz Schafftenau using 10 mL test volumes. Submit the qualification report as a CBE-0 supplement in accordance with 21 CFR 601.12(c)(5).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-6 To qualify the bioburden test for the (b) (4) using the (b) (4) and implement the new bioburden test method. Submit the qualification report as a CBE-30 supplement in accordance with 21 CFR 601.12(c).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-7 To develop and implement a comprehensive and robust control strategy to control for effector function of adalimumab-adaz drug substance at release. Submit the proposed specification as a Prior Approval Supplement in accordance with 21 CFR 601.12(b).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-8 To implement an apoptosis inhibition assay for release and shelf life testing of adalimumab-adaz drug substance and drug product. Submit the proposed

BLA 761071
Page 7

specification as a Prior Approval Supplement in accordance with 21 CFR 601.12(b).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-9 To conduct a drug product (DP) transport validation study during summer time, shipping DP from (b) (4)

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2018

Submit clinical protocols to your IND 115732 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Amundson Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

BLA 761071
Page 8

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

BsUFA II APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

BLA 761071
Page 9

ERG will contact you to schedule a BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Acting Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Prescribing Information
Medication Guide
Instructions for Use
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIKOLAY P NIKOLOV

10/30/2018

Signed under the authority delegated by Dr. Sally Seymour, Acting Division Director,
DPARP.

EXHIBIT 14

BLA Number	Applicant Name	Proprietary Name	Proper Name	Patent Number	Patent Expiration Date
125031	Amgen Inc.	Neulasta	pegfilgrastim	9,856,287	June 21, 2030
125057	AbbVie Inc.	Humira	adalimumab	9,315,574	April 21, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,290,568	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,284,371	September 13, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,284,370	June 10, 2028
125057	AbbVie Inc.	Humira	adalimumab	9,273,132	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,266,949	May 13, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,234,032	September 13, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,187,559	April 11, 2025
125057	AbbVie Inc.	Humira	adalimumab	9,181,572	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,181,337	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,150,645	May 13, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,102,723	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,096,666	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,090,867	September 13, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,090,689	July 18, 2023
125057	AbbVie Inc.	Humira	adalimumab	9,090,688	April 26, 2032
125057	AbbVie Inc.	Humira	adalimumab	9,085,620	July 18, 2023
125057	AbbVie Inc.	Humira	adalimumab	9,085,619	November 28, 2028
125057	AbbVie Inc.	Humira	adalimumab	9,085,618	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,067,992	July 18, 2023
125057	AbbVie Inc.	Humira	adalimumab	9,062,106	April 26, 2032
125057	AbbVie Inc.	Humira	adalimumab	9,061,005	April 11, 2025
125057	AbbVie Inc.	Humira	adalimumab	9,550,826	November 14, 2034
125057	AbbVie Inc.	Humira	adalimumab	8,999,337	February 6, 2031
125057	AbbVie Inc.	Humira	adalimumab	11,191,834	November 28, 2028
125057	AbbVie Inc.	Humira	adalimumab	11,167,030	November 28, 2028
125057	AbbVie Inc.	Humira	adalimumab	11,083,792	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,957,318	April 26, 2032
125057	AbbVie Inc.	Humira	adalimumab	9,913,902	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,708,400	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,683,033	April 26, 2032
125057	AbbVie Inc.	Humira	adalimumab	9,669,093	June 10, 2028
125057	AbbVie Inc.	Humira	adalimumab	9,624,295	March 31, 2031
125057	AbbVie Inc.	Humira	adalimumab	9,328,165	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	9,546,212	June 5, 2022
125057	AbbVie Inc.	Humira	adalimumab	9,522,953	April 26, 2032
125057	AbbVie Inc.	Humira	adalimumab	9,512,216	April 11, 2025
125057	AbbVie Inc.	Humira	adalimumab	9,505,834	April 26, 2032
125057	AbbVie Inc.	Humira	adalimumab	9,499,616	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,499,614	March 14, 2034
125057	AbbVie Inc.	Humira	adalimumab	9,359,434	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,346,879	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	9,339,610	January 24, 2032
125057	AbbVie Inc.	Humira	adalimumab	9,334,319	March 14, 2033
125057	AbbVie Inc.	Humira	adalimumab	8,992,926	June 5, 2022
125057	AbbVie Inc.	Humira	adalimumab	6,805,686	May 6, 2023
125057	AbbVie Inc.	Humira	adalimumab	8,231,876	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,420,081	January 13, 2030
125057	AbbVie Inc.	Humira	adalimumab	8,663,945	September 13, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,708,968	January 24, 2032
125057	AbbVie Inc.	Humira	adalimumab	8,715,664	July 24, 2027

BLA Number	Applicant Name	Proprietary Name	Proper Name	Patent Number	Patent Expiration Date
125057	AbbVie Inc.	Humira	adalimumab	8,808,700	May 16, 2026
125057	AbbVie Inc.	Humira	adalimumab	8,883,156	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,889,136	October 9, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,895,009	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,906,372	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,906,646	September 13, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,906,373	July 18, 2023
125057	AbbVie Inc.	Humira	adalimumab	8,986,693	April 11, 2025
125057	AbbVie Inc.	Humira	adalimumab	8,974,790	June 5, 2022
125057	AbbVie Inc.	Humira	adalimumab	8,961,974	April 11, 2025
125057	AbbVie Inc.	Humira	adalimumab	8,961,973	April 11, 2025
125057	AbbVie Inc.	Humira	adalimumab	8,926,975	June 8, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,916,153	April 4, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,911,964	September 13, 2027
125057	AbbVie Inc.	Humira	adalimumab	8,911,737	June 5, 2022
125085	Genentech, Inc.	Avastin	bevacizumab	10,208,355	July 14, 2035
125085	Genentech, Inc.	Avastin	bevacizumab	9,714,293	August 6, 2030
125085	Genentech, Inc.	Avastin	bevacizumab	10,017,732	March 14, 2034
125085	Genentech, Inc.	Avastin	bevacizumab	10,011,856	May 26, 2031
125085	Genentech, Inc.	Avastin	bevacizumab	9,795,672	May 28, 2024
125085	Genentech, Inc.	Avastin	bevacizumab	9,487,809	January 14, 2032
125085	Genentech, Inc.	Avastin	bevacizumab	9,441,035	April 23, 2034
125085	Genentech, Inc.	Avastin	bevacizumab	8,574,869	July 8, 2028
125085	Genentech, Inc.	Avastin	bevacizumab	8,512,983	January 4, 2031
125085	Genentech, Inc.	Avastin	bevacizumab	8,460,895	March 11, 2029
125085	Genentech, Inc.	Avastin	bevacizumab	7,485,704	March 8, 2025
125085	Genentech, Inc.	Avastin	bevacizumab	10,336,983	July 31, 2035
125085	Genentech, Inc.	Avastin	bevacizumab	10,274,466	July 11, 2035
125085	Genentech, Inc.	Avastin	bevacizumab	11,078,294	July 8, 2028
125085	Genentech, Inc.	Avastin	bevacizumab	10,982,003	August 6, 2030
125085	Genentech, Inc.	Avastin	bevacizumab	10,906,986	July 8, 2028
125085	Genentech, Inc.	Avastin	bevacizumab	10,906,934	October 12, 2033
125085	Genentech, Inc.	Avastin	bevacizumab	10,829,732	March 14, 2034
125085	Genentech, Inc.	Avastin	bevacizumab	10,704,071	August 18, 2031
125085	Genentech, Inc.	Avastin	bevacizumab	10,676,710	March 14, 2034
125085	Genentech, Inc.	Avastin	bevacizumab	10,662,237	May 26, 2031
125085	Genentech, Inc.	Avastin	bevacizumab	10,513,697	September 17, 2032
125104	Biogen Inc.	Tysabri	natalizumab	10,444,234	January 11, 2031
125104	Biogen Inc.	Tysabri	natalizumab	10,844,416	June 1, 2036
125104	Biogen Inc.	Tysabri	natalizumab	8,809,049	May 22, 2031
125104	Biogen Inc.	Tysabri	natalizumab	9,696,307	February 5, 2030
125104	Biogen Inc.	Tysabri	natalizumab	10,705,095	April 4, 2026
125104	Biogen Inc.	Tysabri	natalizumab	9,709,575	April 4, 2026
125104	Biogen Inc.	Tysabri	natalizumab	8,871,449	April 12, 2026
125104	Biogen Inc.	Tysabri	natalizumab	8,124,350	August 2, 2027
125104	Biogen Inc.	Tysabri	natalizumab	11,287,423	January 11, 2031
125104	Biogen Inc.	Tysabri	natalizumab	11,268,119	February 21, 2036
125104	Biogen Inc.	Tysabri	natalizumab	9,316,641	January 9, 2032
125104	Biogen Inc.	Tysabri	natalizumab	11,280,794	May 27, 2034
125104	Biogen Inc.	Tysabri	natalizumab	10,677,803	May 27, 2034
125104	Biogen Inc.	Tysabri	natalizumab	10,119,976	May 27, 2034
125104	Biogen Inc.	Tysabri	natalizumab	11,292,845	February 28, 2027
125104	Biogen Inc.	Tysabri	natalizumab	10,233,245	February 28, 2027
125104	Biogen Inc.	Tysabri	natalizumab	9,493,567	March 5, 2027

BLA Number	Applicant Name	Proprietary Name	Proper Name	Patent Number	Patent Expiration Date
125104	Biogen Inc.	Tysabri	natalizumab	9,994,968	August 19, 2034
125104	Biogen Inc.	Tysabri	natalizumab	10,676,772	August 19, 2034
125104	Biogen Inc.	Tysabri	natalizumab	11,124,760	August 27, 2035
125104	Biogen Inc.	Tysabri	natalizumab	9,096,879	January 7, 2031
125104	Biogen Inc.	Tysabri	natalizumab	7,759,117	June 21, 2024
125104	Biogen Inc.	Tysabri	natalizumab	7,157,276	June 21, 2024
125104	Biogen Inc.	Tysabri	natalizumab	9,109,015	August 13, 2031
125104	Biogen Inc.	Tysabri	natalizumab	9,212,379	November 28, 2030
125104	Biogen Inc.	Tysabri	natalizumab	8,318,416	January 20, 2031
125104	Biogen Inc.	Tysabri	natalizumab	10,308,706	February 5, 2031
125104	Biogen Inc.	Tysabri	natalizumab	9,005,926	October 1, 2030
125104	Biogen Inc.	Tysabri	natalizumab	10,590,454	May 11, 2032
125104	Biogen Inc.	Tysabri	natalizumab	9,790,533	May 11, 2032
125104	Biogen Inc.	Tysabri	natalizumab	9,562,252	May 11, 2033
125104	Biogen Inc.	Tysabri	natalizumab	10,023,831	March 17, 2035
125156	Genentech, Inc.	Lucentis	ranibizumab	6,828,121	July 8, 2022
125156	Genentech, Inc.	Lucentis	ranibizumab	6,716,602	November 1, 2021
125156	Genentech, Inc.	Lucentis	ranibizumab	6,921,659	October 17, 2023
125156	Genentech, Inc.	Lucentis	ranibizumab	8,383,773	December 13, 2023
125156	Genentech, Inc.	Lucentis	ranibizumab	8,574,869	July 8, 2028
125156	Genentech, Inc.	Lucentis	ranibizumab	9,688,775	December 31, 2022
125156	Genentech, Inc.	Lucentis	ranibizumab	10,017,732	March 14, 2034
125156	Genentech, Inc.	Lucentis	ranibizumab	10,112,994	November 5, 2035
125156	Genentech, Inc.	Lucentis	ranibizumab	10,421,984	September 19, 2033
125156	Genentech, Inc.	Lucentis	ranibizumab	9,765,379	March 10, 2034
125156	Genentech, Inc.	Lucentis	ranibizumab	10,829,732	March 14, 2034
125261	Janssen Biotech, Inc.	Stelara	ustekinumab	6,902,734	September 25, 2023
125261	Janssen Biotech, Inc.	Stelara	ustekinumab	8,852,889	July 6, 2032
125261	Janssen Biotech, Inc.	Stelara	ustekinumab	9,217,168	March 14, 2033
125261	Janssen Biotech, Inc.	Stelara	ustekinumab	9,475,858	July 6, 2032
125261	Janssen Biotech, Inc.	Stelara	ustekinumab	9,663,810	March 14, 2033
125261	Janssen Biotech, Inc.	Stelara	ustekinumab	10,961,307	September 24, 2039
125276	Genentech, Inc.	Actemra	tocilizumab	10,231,981	November 19, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	7,521,052	April 28, 2024
125276	Genentech, Inc.	Actemra	tocilizumab	10,017,732	March 15, 2033
125276	Genentech, Inc.	Actemra	tocilizumab	9,902,777	May 28, 2025
125276	Genentech, Inc.	Actemra	tocilizumab	9,750,752	September 1, 2031
125276	Genentech, Inc.	Actemra	tocilizumab	9,714,293	January 9, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	9,630,988	June 13, 2032
125276	Genentech, Inc.	Actemra	tocilizumab	9,539,263	November 8, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	8,734,800	March 24, 2025
125276	Genentech, Inc.	Actemra	tocilizumab	8,709,409	June 22, 2024
125276	Genentech, Inc.	Actemra	tocilizumab	8,617,550	September 11, 2025
125276	Genentech, Inc.	Actemra	tocilizumab	8,580,264	November 8, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	8,574,869	July 9, 2027
125276	Genentech, Inc.	Actemra	tocilizumab	8,568,720	November 5, 2029
125276	Genentech, Inc.	Actemra	tocilizumab	8,512,983	January 9, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	8,398,980	September 27, 2026
125276	Genentech, Inc.	Actemra	tocilizumab	10,982,003	August 11, 2029
125276	Genentech, Inc.	Actemra	tocilizumab	7,332,289	August 4, 2023
125276	Genentech, Inc.	Actemra	tocilizumab	11,377,678	October 25, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	11,359,026	December 26, 2028
125276	Genentech, Inc.	Actemra	tocilizumab	11,136,610	October 25, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	11,136,375	October 14, 2028

BLA Number	Applicant Name	Proprietary Name	Proper Name	Patent Number	Patent Expiration Date
125276	Genentech, Inc.	Actemra	tocilizumab	11,078,294	July 9, 2027
125276	Genentech, Inc.	Actemra	tocilizumab	11,021,728	October 25, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	11,008,394	December 26, 2028
125276	Genentech, Inc.	Actemra	tocilizumab	10,336,983	July 31, 2035
125276	Genentech, Inc.	Actemra	tocilizumab	10,874,677	March 4, 2031
125276	Genentech, Inc.	Actemra	tocilizumab	10,829,732	March 15, 2033
125276	Genentech, Inc.	Actemra	tocilizumab	10,744,201	April 28, 2024
125276	Genentech, Inc.	Actemra	tocilizumab	10,676,710	March 15, 2033
125276	Genentech, Inc.	Actemra	tocilizumab	10,662,237	May 26, 2030
125276	Genentech, Inc.	Actemra	tocilizumab	10,590,164	March 19, 2032
125276	Genentech, Inc.	Actemra	tocilizumab	10,501,769	October 25, 2030
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,481,901	May 29, 2034
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,388,447	April 20, 2032
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,359,435	May 22, 2027
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,328,134	February 20, 2034
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,320,816	November 14, 2030
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,133,493	April 20, 2032
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,012,178	August 5, 2031
125320	Amgen Inc.	Prolia and Xgeva	denosumab	8,058,418	November 30, 2023
125320	Amgen Inc.	Prolia and Xgeva	denosumab	7,928,205	February 12, 2027
125320	Amgen Inc.	Prolia and Xgeva	denosumab	7,427,659	March 15, 2025
125320	Amgen Inc.	Prolia and Xgeva	denosumab	7,364,736	February 19, 2025
125320	Amgen Inc.	Prolia and Xgeva	denosumab	9,228,168	January 19, 2030
125320	Amgen Inc.	Prolia and Xgeva	denosumab	10,513,723	December 9, 2034
125320	Amgen Inc.	Prolia and Xgeva	denosumab	11,434,514	May 29, 2034
125320	Amgen Inc.	Prolia and Xgeva	denosumab	11,299,760	October 30, 2034
125320	Amgen Inc.	Prolia and Xgeva	denosumab	11,254,963	December 9, 2034
125320	Amgen Inc.	Prolia and Xgeva	denosumab	11,130,980	April 5, 2035
125320	Amgen Inc.	Prolia and Xgeva	denosumab	11,098,079	July 21, 2037
125320	Amgen Inc.	Prolia and Xgeva	denosumab	11,077,404	May 13, 2035
125320	Amgen Inc.	Prolia and Xgeva	denosumab	10,167,492	December 1, 2035
125320	Amgen Inc.	Prolia and Xgeva	denosumab	10,894,972	May 29, 2034
125320	Amgen Inc.	Prolia and Xgeva	denosumab	10,822,630	December 1, 2035
125320	Amgen Inc.	Prolia and Xgeva	denosumab	10,583,397	July 28, 2035
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,084,865	June 14, 2027
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,066,458	June 14, 2027
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,053,280	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,973,879	May 17, 2039
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,927,342	August 3, 2036
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,918,754	March 6, 2038
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,905,786	March 6, 2038
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,888,601	January 11, 2032
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	D906,102	December 29, 2035
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,857,231	Disclaimer filed on March 14, 2022
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,857,205	January 11, 2032
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,828,354	January 11, 2032
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,669,594	February 12, 2037
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,464,992	June 14, 2027
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,415,055	June 4, 2028
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,406,226	March 22, 2026
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	10,130,681	January 11, 2032
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	9,816,110	October 21, 2035
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	9,669,069	January 11, 2032
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	9,254,338	May 22, 2032

BLA Number	Applicant Name	Proprietary Name	Proper Name	Patent Number	Patent Expiration Date
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	9,222,106	June 4, 2028
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	7,070,959	June 16, 2023
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	D858,754	September 3, 2034
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,459,373	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,104,715	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,485,770	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,478,588	July 25, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,472,861	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,459,374	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,439,758	June 4, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,433,186	December 12, 2038
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	D961,377	August 23, 2037
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	D961,376	August 23, 2037
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,332,771	March 14, 2034
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,306,135	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,299,532	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,253,572	January 11, 2032
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,186,625	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,174,283	August 18, 2040
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,160,918	July 29, 2039
125387	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	D934,069	October 26, 2036
125388	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,505,593	August 18, 2040
125389	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,548,932	August 18, 2040
125390	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,555,176	January 27, 2040
125391	Regeneron Pharmaceuticals, Inc.	Eylea	aflibercept	11,559,564	January 11, 2032
761044	Janssen Biotech, Inc.	Stelara	ustekinumab	9,217,168	March 14, 2033
761044	Janssen Biotech, Inc.	Stelara	ustekinumab	8,852,889	July 6, 2032
761044	Janssen Biotech, Inc.	Stelara	ustekinumab	9,475,858	July 6, 2032
761044	Janssen Biotech, Inc.	Stelara	ustekinumab	9,663,810	March 14, 2033
761044	Janssen Biotech, Inc.	Stelara	ustekinumab	10,961,307	September 24, 2039
761044	Janssen Biotech, Inc.	Stelara	ustekinumab	6,902,734	September 25, 2023

EXHIBIT 15

Department of State: Division of Corporations

[Allowable Characters](#)

HOME

Entity Details

THIS IS NOT A STATEMENT OF GOOD STANDING

File Number: 7944830 Incorporation Date / Formation Date: 7/30/2020 (mm/dd/yyyy)
Entity Name: SANDOZ INC.
Entity Kind: Corporation Entity Type: General
Residency: Domestic State: DELAWARE

REGISTERED AGENT INFORMATION

Name: CORPORATION SERVICE COMPANY
Address: 251 LITTLE FALLS DRIVE
City: WILMINGTON County: New Castle
State: DE Postal Code: 19808
Phone: 302-636-5401

Additional Information is available for a fee. You can retrieve Status for a fee of \$10.00 or more detailed information including current franchise tax assessment, current filing history and more for a fee of \$20.00.

Would you like ☐ Status ☐ Status, Tax & History Information

Submit

View Search Results

New Entity Search

For help on a particular field click on the Field Tag to take you to the help area.

[site map](#) | [privacy](#) | [about this site](#) | [contact us](#) | [translate](#) | [delaware.gov](#)